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STRUCTURE OF THE MALARIAL PARASITES.

By JESSE W. LAZEAR, M. D.

(Plate I.)

When stained with methylene blue the greater part of the malarial parasite takes on a rather pale blue color. It was, however, early noticed that there is in most organisms a small round or ovoid portion which remains unstained. This portion can often be distinguished in the fresh specimen, as a vacuole-like area free from pigment.

In 1891, Romanowsky (1), in a study of six cases of tertian malarial fever, demonstrated a peculiar body within the vacuole-like area, which took on a deep carmine-violet color when treated with methylene blue and eosin combined in certain definite proportions. This body he believed to consist of nuclear material.

In 1895, Gautier (2), studying the malarial fevers of the Caucasus, found that this nuclear material or chromatin could be stained only when the methylene blue and eosin of certain factories and certain commercial marks were used. He obtained the best results with methylene blue B. G. N of the Badische-Soda-Anilin Fabrik, and eosin of the same factory.

Ziemann (3), in 1898, published the results of a long series of similar experiments. His best results were obtained with methylene blue, medicinally pure, and eosin A. G. and B. A. of the Hoechst factory. These stains were also used by Bastianelli and Bignami (4).

Nocht (5) of Hamburg found that by combining polychrome methylene blue with a saturated aqueous solution of ordinary methylene blue he could get the same results with blues of all makes.

At the suggestion of Dr. Thayer, I endeavored to carry out the methods of these observers, a work which has not as yet been done in this country. I made repeated trials with the stains recommended by Gautier with constantly negative results. The explanation of this failure is, I believe, that my stains, although

bearing the same commercial marks, were really not identical with those used by Gautier.

With the Ziemann stains I was able to get good results. This method, however, is extremely complicated and tedious, involving the expenditure of much time and material. Numerous trial solutions have to be made, and tested by staining smears for various lengths of time.

The method of Nocht was far more satisfactory. It is carried out as follows: Polychrome methylene blue is carefully neutralized. This is done by first adding dilute acetic acid until the solution is acid. When litmus paper is dipped into the solution, it is colored by the methylene blue, but on the margin of the moist portion the acidity causes a red line to appear. The solution is now brought back to the neutral point by the addition of more polychrome methylene blue until the red line fails to appear on the blue litmus paper. The polychrome methylene blue may be obtained already prepared. It can, however, be readily made by heating for several hours, on a water-bath, a solution consisting of—

Methylene blue	1 part.
Caustic soda	1 "
Water (distilled)	100 "

After cooling, the solution is to be filtered.

To this polychrome methylene blue an equal quantity of distilled water is added, and then, a saturated solution of ordinary methylene blue, until the red color is completely lost, the solution appearing simply blue. For this purpose about one part of the saturated aqueous solution to ten parts of the diluted polychrome solution will be used.

A solution of eosin is now prepared, according to Nocht, by adding three or four drops of a one per cent aqueous solution of eosin to one or two cc. of water. This is practically a 0.2 per cent solution; it can be made up in quantity. To three or four cc. of the eosin solution, Nocht adds the methylene-blue solution until the red color disappears. At this point a fine precipitate is thrown down, and a scum begins to form on the surface.

I found it more satisfactory to keep the two solutions in burettes, as is done by Bastianelli and Bignami. The solutions may be

made in large quantity, and the proper proportions in which they should be mixed may be determined once for all by a few experiments. The methylene-blue solution varies a great deal in the amount of the unknown nucleus-staining material which it may contain. One solution may require three parts of the eosin solution to each part of the methylene blue, while another, made in the same manner, may require only one part of the eosin solution to three parts of the methylene blue. When the proper proportion is once determined for a given solution, it remains constant.

The eosin and methylene-blue solutions should be mixed immediately before use, and the mixture used only once. When kept a day or two, such a mixture may sometimes give the chromatin stain, but always feebly.

Nocht fixed the blood-smears by placing them in equal parts of absolute alcohol and ether, but I obtained my best results by treating with a one-fourth per cent solution of formalin in 95 per cent alcohol, for one or two minutes. The formalin may be kept in 10 per cent aqueous solution, four or five drops of this being added to 10 cc. of 95 per cent alcohol, just before using.

Before placing the specimen in the staining solution, the scum should be carefully removed by means of filter paper. It is best to use a staining-dish with concave bottom, placing the cover-slip on the bottom with the preparation side down. The specimen is left in the stain for from three to twenty-four hours. The scum should be carefully removed before taking out the cover-glass, as it tends to adhere to the specimen if it comes in contact with it, making the examination difficult or impossible.

I have gone over the technique minutely, as good results are to be obtained only by exact manipulation. When carried out in this manner, this procedure far surpasses all other staining methods for the study of the malarial parasite. Indeed, the method is of considerable diagnostic value. I have seen in Cuba several obscure cases of æstivo-autumnal fevers in which the ring-shaped hyaline bodies were much more easily found in the stained specimens than in the fresh blood.

The chromatin in malarial parasites may also be brought out, though less perfectly, by prolonged staining in hæmatoxylin. Fairly good results may be obtained by leaving the specimens for three days in Ehrlich's Eosin-Hæmatoxylin Mixture.

When stained by Nocht's method the red corpuscles take an eosin color, while the nuclei of all forms of leucocytes and of nucleated red corpuscles show a deep carmine-violet tint. It is interesting to note that the blood platelets show a fine network throughout their structure which takes the chromatin stain. This strengthens the evidence in favor of the view that they are of nuclear origin (Fig. H).

* * * * * * * * * * * * * * * * *

The malarial parasite is made up of a protoplasmic portion which stains blue and a nucleus composed of a peripheral achromatic zone and a central portion made up of chromatin which takes a deep carmine-violet color.

The Tertian Parasite.

The structure of the tertian parasite was studied in specimens taken at various periods in the cycle of development. The most satisfactory method was to make a series of specimens by taking blood at frequent intervals in a case of single tertian infection. In this way the structure, at all periods, could be easily determined without danger of confusion between two groups of parasites.

The parasite first appears in the red cell as a rounded or apparently ring-shaped body, made up of blue staining protoplasm and a nucleus situated excentrically, as a rule, in the rounded forms and like a signet in the ring-shaped bodies. The nucleus consists of a dense violet staining mass of chromatin in the centre, surrounded by a thin achromatic zone.

During the first twenty-four hours the parasite grows slowly, filling at the end of this period not more than one-third of the red corpuscle. The growth is due to an increase in the protoplasm and the achromatic portion of the nucleus, the chromatin itself becoming irregular or nodular in shape, but showing little or no increase in volume. The parasite becomes more and more irregular in shape as amœboid motion increases, but it often retains traces of the early ring form, a narrow arm being thrown out, encircling apparently a rounded portion of the red corpuscle.

During the second half of the cycle the growth is much more rapid, and at last the parasite nearly or completely fills the swollen red corpuscle. Meanwhile the mass of chromatin breaks up into a

cluster of fine granules which seem to disappear finally just before segmentation. The achromatic portion of the nucleus is also lost. The chromatin soon reappears, scattered through the protoplasm in fine granules, arranged in strands and masses. These become aggregated at first into four or five irregular clusters, and later into from sixteen to twenty dense rounded masses. The protoplasm collects around these masses, and finally the segments become separated from each other, each composed of a mass of chromatin surrounded by a thin achromatic zone and a larger mass of protoplasm lying beside it or partially surrounding it.

The pigment is scattered through the protoplasm up to the beginning of segmentation, when it shows a tendency to be pushed to the periphery and later to collect in one or two masses, usually near the centre. The latter phenomenon evidently follows segmentation, rather than preceding it as one would suppose from the examination of the fresh specimen alone. In other words segmentation is nearly complete before any indication of it is visible without the use of special nuclear staining methods (Fig. A, 1-11).

The forms just described are those which occur in the asexual cycle of development, that which leads to the multiplication of individuals in the body of one host. Besides these, however, there are seen forms which serve to carry the infection to a new host; these are the sexually differentiated bodies—gametes.

The full-grown gametes are intracellular bodies of large size, nearly filling the containing red corpuscle. They have a large nucleus composed of a cluster of fine chromatin granules in a large, pale achromatic area. These bodies correspond to the crescentic forms of the æstivo-autumnal parasite. Like the crescents, they may be found in the blood both during the paroxysms and between them. In some of my series, made throughout the cycle in single tertian infections, I was able to demonstrate gametes in every specimen.

Bastianelli and Bignami believe, apparently, that the bodies with finely granular chromatin, described above as immediately preceding segmentation in the asexual cycle, really represent an early stage in the development of gametes. They do not recognize the gradual disintegration of the chromatin as a part of the regular cycle, therein differing from Gautier and Ziemann.

There are several objections to the view of Bastianelli and Bignami. The finely granular chromatin begins to appear in forms which have attained nearly half the size of the corpuscle. No smaller examples are to be seen. A more serious objection, however, lies in the fact that, at a certain stage, all the parasites may have this form. I have specimens in sharply marked cases of single tertian fever, in which there are large numbers of parasites, all of which have the finely granular chromatin. In these cases specimens taken a few hours later show many segmenting bodies, suggesting strongly that the parasites showing a fine subdivision of the nuclear chromatin have gone on to segmentation, forming, thus, part of the regular cycle.

It is possible, as Bastianelli and Bignami suggest, that the early stages in the development of the gametes take place in the bone-marrow, as this is the principal seat of formation of their apparent analogues, the crescent bodies in æstivo-autumnal fever; it is not improbable that the history of the crescent and the tertian gametes is closely analogous (Fig. B, 1, 2).

The Quartan Parasite.

The young quartan parasite is of about the same size as the young tertian organism, while the structure of the nucleus and protoplasm is similar. The chromatin mass is, however, not so dense and rounded, but shows irregularities, as if it were made up of granules. Growth is slower than in the tertian organism, but the chromatin shows a tendency to break up into granules earlier in the cycle. During most of the cycle it is seen as a cluster of very fine granules. The protoplasm shows less irregularity of contour, owing to the limited amœboid movements of the quartan parasite. The shape is usually ovoid, but often in dried specimens the parasite extends across the red corpuscle like a broad band. The pigment is sometimes coarser than in the tertian body, and early shows a tendency to seek the periphery. The containing red corpuscle progressively diminishes in size, and stains more deeply with eosin. The chromatin granules gradually disappear, but chromatin soon reappears in irregular clusters of granules, which finally collect into eight or ten well-defined masses, each accompanied by a portion of the protoplasm. The mass of chromatin is not so dense as in the tertian parasite, and usually appears to be

made up of an agglomeration of granules. The pigment collects in a central mass as in the tertian form (Fig. C, 1-5).

The Æstivo-Autumnal Parasite.

Although two types of æstivo-autumnal parasite have been described by the Italian authors, one having a cycle of development of twenty-four hours, and the other of forty-eight, yet I have observed only organisms with a tertian cycle.

In the peripheral blood one is able to find, as a rule, only the gametes (crescentic and ovoid bodies) and the earlier stages of the asexual cycle. The rest of this cycle was studied in blood obtained by aspiration from the spleen during life, or in smears from the spleen and bone-marrow taken at autopsy.

At the earliest stage the parasite is usually somewhat smaller than the tertian or quartan organism at a similar period, and almost invariably has a circular form. The chromatin is seen in a rounded mass, in two or three small masses, or as a short filament. While in the peripheral blood, the parasite is usually free from pigment, though in several cases organisms were observed which contained a few fine granules.

Material was not at hand for so thorough a study of the later stages of development of the æstivo-autumnal parasite, as was made of the tertian and quartan organisms. The process of breaking up of the chromatin was not observed, but segmenting forms were seen in large numbers. The chromatin was arranged in from ten to twenty small rounded, dense masses. The blue staining protoplasm was not so evident, and was probably smaller in amount than in the segmenting bodies of the tertian and quartan parasites. At segmentation the parasite occupies not more than half the red corpuscle. The pigment is gathered in a single dense mass at the centre (Fig. D, 1-4).

Two types of crescentic body were made out. In one the chromatin consists of a cluster of fine granules situated in a round pale space at one end of the clump of pigment and partially or completely surrounded by it. In the other the fine granules of chromatin are scattered among the pigment particles. In some of the crescents no chromatin at all is to be seen; it may, however, be present, but concealed by the pigment. The central portion of all

the crescents stains more palely with the blue than do the horns (Fig. E, 1-3).

Specimens were prepared for the study of flagellation by leaving two cover-slips with the blood-film between them, for lengths of time varying from five minutes to an hour, protected from evaporation in a small closed chamber. They were then taken from the chamber, pulled apart at once, and allowed to dry. On staining and examining such specimens it was found that some of the crescents had undergone changes which varied according to the length of time the cover-slips had been left in contact. At first they become changed into spherical bodies in which the chromatin becomes more prominent than it was in the crescent.

Two types of spherical body are found. One form is smaller than a red corpuscle, perfectly spherical in shape, with pigment scattered throughout. The chromatin appears at first in the centre in a large irregular mass like a tangled thread. Later it becomes arranged in four or five dense masses near the periphery. At the next stage, flagella may be seen to have developed from these masses of chromatin. This, then, is evidently the male body or microgametocyte. The flagellum consists of a strand of chromatin with nodular masses at the distal end, or along its course. Sometimes a bluish envelope of protoplasm may be made out (Fig. G, 1-5).

The second type of spherical body is two or three times as large as the first; it is not, as a rule, perfectly spherical, but often appears somewhat triangular in shape. There was abundant blue-staining protoplasm, while the pigment is arranged in a more or less perfect circle. The chromatin appeared as a single mass in a clear space situated at the periphery and surrounded by the ring of pigment. These forms never apparently give rise to flagella; they probably represent the female bodies—*macrogametes.* They can be recognized in the fresh unstained blood by their size as well as by the ring-like arrangement of the pigment.

It was into a body answering to this description that MacCallum observed the penetration of a flagellum. The structure of these elements resembles that of the macrogametes in Laverania danilewskyi as described by Opie (6) (Fig. F, 1-3).

In my specimens the microgametocytes were found only when the cover-slips had been left in contact for a short time, five to

fifteen minutes. Active flagellating forms were most numerous at from fifteen to thirty minutes. The macrogametes were found both early and late, but in largest numbers at from fifteen to forty minutes. The actual penetration of a microgamete into a macrogamete was not observed, nor was any structure found which was to be recognized as a fertilized macrogamete. This, however, is not surprising when one considers the small number of parasites found in human blood.

The blood of crows infected with Laverania danilewskyi and containing enormous numbers of parasites was also prepared in the manner described above.

The fertilized macrogamete or pseudovermicule, as observed by MacCallum (7) in the fresh blood, was readily found. It is a pear-shaped body, with a collection of pigment granules at the blunt end, usually contained in a small rounded appendage. There is a nucleus made up of a cluster of chromatin granules situated at the centre of the pear-shaped body (Fig. I, 1-2).

Specimens were prepared to show the process of flagellation in the tertian parasite. The gametes become extracellular soon after the blood is drawn. They assume a spherical shape and undergo changes quite like those described for the æstivo-autumnal parasite.

Havana, July, 1900.

1. Romanowsky.—St. Petersburger med. Woch., 1891, Nos. 34 and 35.
2. Gautier.—Zeitschrift für Hygiene, XXVIII, 439.
3. Ziemann.—Ueber Malaria und andere Blutparasiten. 8vo. Jena, 1898.
4. Bastianelli and Bignami.—Annali D' Igiene Sperimentale, 1899, Vol. IX, Fasc. III.
5. Nocht.—Centralblatt für Bacteriologie, XXIV, 839.
6. Opie.—Journal of Experimental Medicine, III, 79.
7. MacCallum.—Journal of Experimental Medicine, III, 117.
8. Zettnow.—Zeitschrift für Hygiene, XXX, 1.

DESCRIPTION OF PLATE I.

Fig. A. 1–11 Tertian parasites, asexual generation.

" B. 1–2 Tertian parasites, gametes.

" C. 1–5 Quartan parasites, asexual generation.

" D. 1–4 Æstivo-autumnal parasites, asexual generation.

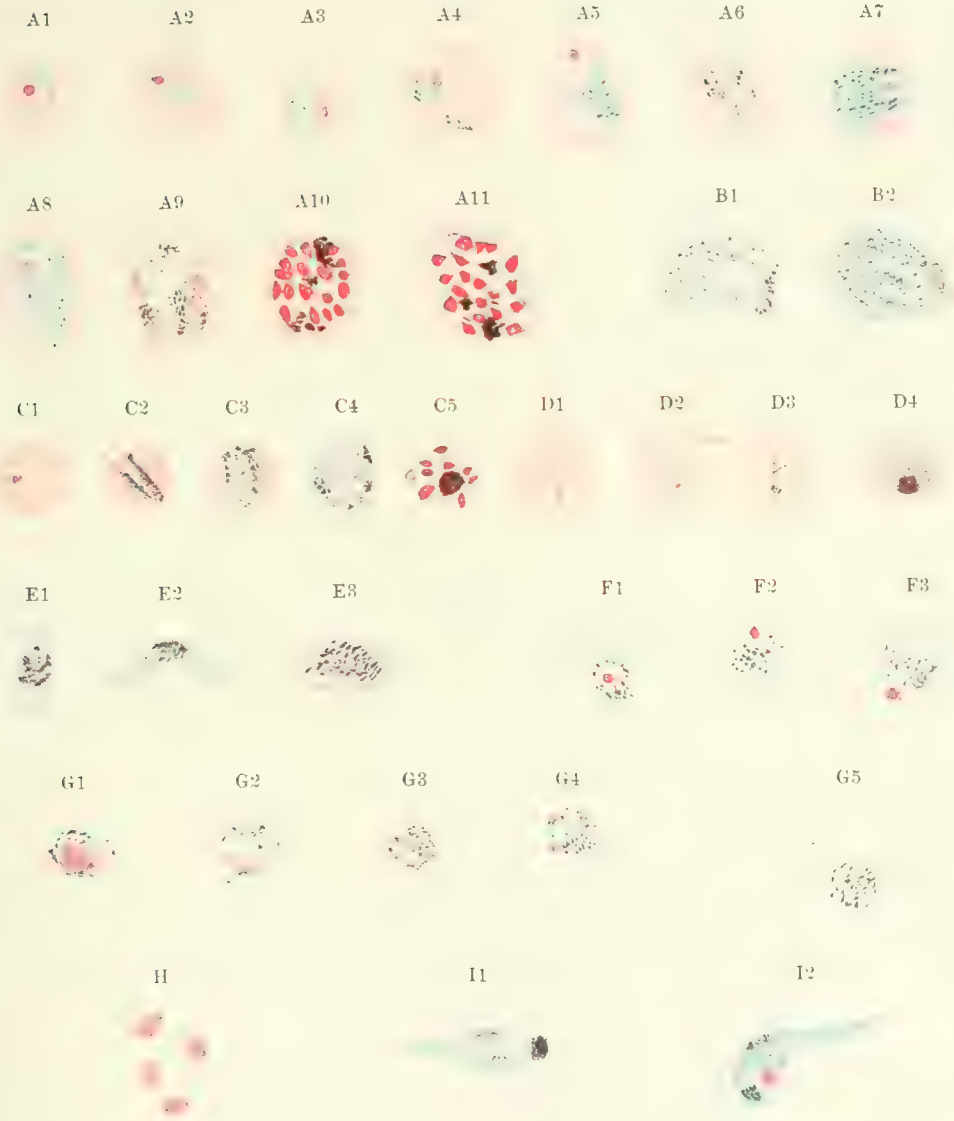
" E. 1–3 Æstivo-autumnal parasites, crescentic bodies.

" F. 1–3 Æstivo-autumnal parasites, macrogametes.

" G. 1–5 Æstivo-autumnal parasites, microgametocytes.

" H. Blood platelets.

" I. 1–2 Pseudovermiculus. Laverania danilewskyi. From blood of crow.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THE BACTERIOLOGY OF CYSTITIS, PYELITIS AND PYELONEPHRITIS IN WOMEN, WITH A CONSIDERATION OF THE ACCESSORY ETIOLOGICAL FACTORS IN THESE CONDITIONS, AND OF THE VARIOUS CHEMICAL AND MICROSCOPICAL QUESTIONS INVOLVED.

By THOMAS R. BROWN, M. D.

Although Pasteur in 1859 suggested that cystitis was of bacterial origin, a view which was subsequently held by Traube, Niemeyer, Neubauer, Vogel and others, it is only within a comparatively short time that the mass of clinicians have agreed to this idea; in fact even in many of the modern text-books on medicine most absurd and erroneous views are expressed regarding the etiology and general characteristics of cystitis—ideas which could be refuted by a few minutes' study with the microscope and with the appliances of the most poorly equipped clinical laboratory.

Within the past ten years, however, the bacteriological nature of cystitis, pyelitis and pyelonephritis has been placed upon a firm foundation by the work of Rovsing, Melchior, Guyon, Krogius, Schnitzler, Albarran, Hallé and others; and it must be but a comparatively short time before these views are held by the great majority of practicing physicians and surgeons, and *ipso facto*, the rational treatment of such conditions generally adopted.

There are, however, various differences of opinion among the bacteriologists mentioned above regarding the microorganisms commonly found in these infections, the method of study of the cases brought to their notice and the interpretation of the facts discovered, which in turn have brought about considerable discussion, unnecessarily acrimonious in many cases.

The object of these researches of mine has been to definitely determine, as far as lay in my power, the bacterial flora of the infections of the urinary tract in women; to discuss the other factors which may play a part in the etiology of such infections; to note

the various modes of entrance of the bacteria into the urinary organs; to formulate, if possible, certain rules regarding the relationship between the species of bacteria and the clinical picture presented; to suggest from these findings the line of therapy to be carried out; and to note carefully any details in the cases, individually and collectively, that might tend to throw light upon the moot points of this question or open up new lines of thought. This work differs from any of the preceding researches, *first*, in the fact that the work has been done exclusively upon the urinary infections of *women*; *second*, in that an unusual opportunity has been furnished to study the etiology of these infections, as many of the cases were post-operative and could be most carefully studied before, during and after the infection; *third*, in the fact that in all the cases of renal infection the urine was obtained directly from the kidney by catheterization of the ureters; and *fourth*, in that a careful cystoscopic examination was made in all the chronic cases and most of the acute cases, so that no possible mistake could arise in the diagnosis of the condition.

This work has been carried on during a space of two years, during which time upwards of one hundred cases, besides numerous controls, have been examined by the methods shortly to be described.

For the procuring of the specimens of urine from which these studies are made and the cystoscopic examinations, I am indebted to Dr. Kelly, whom I wish to thank sincerely for his unfailing kindness in this connection.

In this article I shall discuss in order—

I. The method of obtaining the urine aseptically.
II. The chemical and microscopical study of the urine.
III. The bacteriological study of the urine.
IV. The cases of acute cystitis.
V. The cases of chronic cystitis.
VI. The cases of tuberculous cystitis which have been considered separately for obvious reasons.
VII. The cases with symptoms suggestive of cystitis, but with no infection.
VIII. The cases of acute pyelitis and pyelonephritis.
IX. The cases of chronic pyelitis and pyelonephritis.
X. The cases of tuberculous pyelitis and pyelonephritis.

Under the separate headings will be discussed the mode of entrance of the infection, and other etiological factors in the production of this condition, while under Section IV a short note will be found regarding *bacteriuria*,[1] and under Section IX some observations on the relation between calculus and infection. Section XI will contain a brief review of the bacteriological, chemical and etiological findings in our series, while in Section XII a short review of the bacteriological findings of other observers will be given; certain peculiarities of various microorganisms met with will be discussed in Section XIII, as well as a few observations on the agglutination of the microorganisms found in cystitis and pyelitis by the serum of the patient; while in Section XIV a few therapeutic suggestions directly dependent upon the bacteriological and chemical findings will be found.

The number of cases in my series is exactly 100, divided as follows, the tuberculous cases being considered separately:

Cases of acute cystitis, 26.

Cases of chronic cystitis (alone, 24; associated with pyelitis and pyelonephritis, 7), 31.

Cases of tuberculous cystitis (alone, 2; associated with pyelitis and pyelonephritis, 4), 6.

Cases with symptoms suggestive of cystitis, but with no infection (due to urinary hyperacidity, 9; due to other causes, 8), 17.

Cases of acute pyelitis and pyelonephritis, 2.

Cases of chronic pyelitis and pyelonephritis (alone, 4; associated with cystitis, 8), 12.

Cases of tuberculous pyelitis and pyelonephritis (alone, 2; associated with cystitis, 4), 6.

I. *The Method of Obtaining the Urine Aseptically.*

Of course, nothing is more essential than that our method of obtaining the urine should be absolutely aseptic, as otherwise the results of these investigations would be absolutely nil.

This is much easier in the case of woman than in the case of man, due, of course, to the short urethra, the ease of using the

[1] Although, of course, cystitis and true bacteriuria are distinct conditions, this subject is spoken of here to render the subject complete, although we have met with no cases of *pure* bacteriuria in our series.

cystoscope and the ability by means of the latter instrument to catheterize the ureters. Of course, when the cystoscope is used for these purposes a careful examination of the bladder should be made, noting especially the absence or presence of ulceration, congestion and infection, and if present the exact localization of the lesion; the condition of the bladder about the ureteral orifices and the character of the urine flowing from each orifice;[1] the irritability or lack of irritability of the bladder, its distention or contraction, the presence or absence of a "*bas fond*" and of residual urine, the presence or absence of foreign bodies, neoplasms, calculi, pathological communications with abscess cavities or other viscera, etc.

(*a*) *From the Bladder.*

The method of obtaining the urine from the bladder is as follows: The vestibule of the vagina and the mouth of the urethra having been carefully cleansed with bichloride of mercury solution (1: 1000) or boracic acid solution (saturated), followed by sterile water, the lips of the urethra are pulled apart by traction on the labia and a sterilized glass catheter with a sterilized rubber cuff, about 10 cm. long, on its distal end is introduced, the operator only touching the rubber cuff at about its middle. After the urine has flowed for a short time (so that if a few microorganisms from the urethra were introduced, they would be washed out by the first-flowing portion of the urine), the rubber cuff is withdrawn by traction on its distal end and 10 to 20 ccm. of urine collected in a sterile tube, the cotton plug of which is, of course, only removed during the reception of the urine.

To show the adequacy of this simple method of obtaining the urine under aseptic precautions, 52 control experiments have been made upon normal cases and in but one of them was there any contamination whatsoever, in which case one colony, a white staphylococcus, grew in the plate. As we shall see later, in almost all cases of cystitis the microorganisms are present in very large numbers, besides which in every case at least two examinations, made at different times, should be insisted upon.

[1] These are of extreme importance in the study of pyelitis, especially in those cases where the investigator is unable to catheterize the ureters, due either to the foul condition of the bladder and the fear of introducing bacteria into the upper urinary tract or to lack of experience in ureteral catheterization.

We therefore regard the chance of error in this method as infinitesimal.

(*b*) *From the Kidney.*

In our series of cases the urine from the kidney has been obtained directly by catheterization of the ureters, and for that reason we have not used any of the urine separators or segregators, like the Harris instrument. In the male, however, as a general rule, some such instrument will probably have to be employed in order to obtain urine from either kidney.

The only difference between our method of obtaining urine from the kidney and from the bladder is that in the former case a cystoscope is introduced into the bladder, and through this a sterile ureteral catheter with the rubber cuff on its distal end is introduced into the ureter and inserted as far as necessary towards the renal region. Of course great care must be taken that the catheter touches nothing in its course and that the bladder is thoroughly washed out before its introduction, or at least carefully emptied. If there is infection of the bladder great care should be taken in inserting the catheter; the ureteral orifice should be carefully swabbed with a solution of silver nitrate or some other antiseptic fluid and the catheter should be inserted but a short distance into the ureter. It is also of importance that the patient drink considerable water before the examination so that the flow of urine shall be increased.

After the catheter has been introduced the urine is allowed to flow for a few moments (which it does drop by drop normally, but in a steady stream if there is a hydronephrosis or pyelonephrosis), when the rubber cuff is withdrawn and the urine collected as before. The success of this method of obtaining urine from the kidney is shown by the fact that in 32 control experiments carried out either upon perfectly normal individuals or on those with one normal kidney but with pyelitis of the other kidney, and in some cases also with cystitis, only one showed any contamination, and that again was readily recognized as before, only one colony growing from 3 loops of urine; whether this was because of a slight urinary contamination or, as seems more probable, the microbe dropped into the plate from the air while the culture was being made, one cannot say, but the presumptive evidence is in favor of the latter proposition.

II. *The Chemical and Microscopical Study of the Urine.*

After having obtained the urine under aseptic precautions, it is essential that within a very short time (a few minutes if possible) cultures should be made, as well as a careful chemical and microscopical examination either of this specimen or of a larger quantity obtained by catheter at the same time.

(*a*) The reaction of the urine.

The reaction of the urine is of great importance, because it tells us in a broad way, by its acidity, neutrality or alkalinity, something regarding the character of the microorganism causing the infection; although, of course, in a pyelitis caused by a urea-decomposing microbe, if the other kidney is normal, the alkalinity of the urine from the infected side may be neutralized, diminished or overcome by the urine from the other side. Besides the mere reaction of the urine, it is of importance in certain cases with symptoms of cystitis but no infection to determine the degree of the acidity, as we shall see later on. I have done this by titrating 10 ccm. of the freshly obtained urine with 1/10 normal solution of sodium hydroxide, using phenolphthalein as an indicator. Although this method is not so reliable as that of Freund, it requires but little time and furnishes a very fair criterion of the degree of acidity of the urine. When both kidneys are catheterized, the reactions of the two urines should be carefully taken and compared.

(*b*) The specific gravity of the urine.

This is of value because of the almost invariably low specific gravity in cases of pyelonephritis, and also because, in an otherwise normal urine, a constantly low specific gravity is suggestive of hysteria, neurasthenia or other neuroses. Also in cases where both kidneys are catheterized it is of extreme importance to determine the specific gravity and rate of flow of the urine from either kidney (as also the quantity of urea per ccm.), so that we may determine the secretory function of each, an especially important point where removal of one kidney is being considered.

(*c*) The quantity of albumin present.

This, if possible combined with a careful cystoscopic examination, especially as regards the ureteral orifices and the character of the urine flowing from each, is of paramount importance in differentiating pyelitis from cystitis. If the case is one of pure cystitis,

even if there is much ulceration, speaking generally, the amount of albumin present is very small, notwithstanding the pyuria is of high grade, if the examination be made shortly after the voiding of urine; while if the case be one of pure pyelitis the quantity of albumin will be considerably larger, although, perhaps, the grade of pyuria is much lower. If a combination of cystitis and pyelitis be present, the diagnosis is perhaps rendered somewhat more difficult, as also if there is much blood present, but, speaking generally, a marked disproportion between the grade of pyuria and of albuminuria speaks for cystitis, while if there is considerable albumin present, pyelitis is probably present either alone or associated with cystitis. From the urine alone during the past two years we have diagnosed seven cases of pyelitis from the grade of the albuminuria, in four of which there was absolutely no suspicion that the kidney was affected, and subsequent ureteral catheterization and operation proved the correctness of this diagnosis in all seven cases.

Personally, we have not as yet computed quantitatively the amount of albumin to be expected with various grades of renal and vesical infection, but have come to our conclusions more roughly by a consideration of the depth of the sediment in the urine, and the thickness of the albumin ring with nitric acid and the opacity of the urine after boiling and adding acetic acid.

Rosenfeld[1] states that the limit of albumin-content in the severest cystitis is 0.1 per cent; in maximo, 0.15 per cent; in pyelitis it is often 0.3 per cent.

Goldberg[2] counted the red blood-cells and determined the albumin quantitatively; he concluded that if the ratio of the latter amount in percentage to the number of corpuscles per ccm. is more than 1: 30,000, there is a true albuminuria while if less than 1: 30,000 the albumin is accounted for by the blood alone.

(*e*) Microscopical examination.

Before making the microscopical examination of the sediment, we should determine its depth by allowing a certain quantity of urine to stand a certain length of time, as this tells us, in the first place, something regarding the degree and character of the infection, and in the second place furnishes us with a valuable criterion as to the effect of the treatment we are employing.

[1] Berliner klinische Wochenschrift, 1898, xxxiv, 30.

[2] Berliner klinische Wochenschrift, 1895, xxxii, p. 1071.

In the microscopical examination, especial attention should be paid to the presence or absence of microorganisms, and the presence and character of casts, pus-cells, red blood-cells and epithelial cells. As to the microorganisms, their number, motility and morphology should be noted. In cases of blood in the urine when the blood can only be detected microscopically, if the red blood-cells show many chemical and morphological changes, crenation, loss of hemoglobin, etc., it suggests that the bleeding is renal. If the hematuria is of higher grade, however, this is of little value. The crenation or puckering of all the pus-cells also speaks for pyelitis, as also the absence of the large flat epithelial cells of the bladder, which are always found in cystitis. In some cases the small renal and ureteral epithelial cells can be distinctly recognized, especially if present in flakes. As a criterion of the effect of any treatment, the number of pus-cells per 1 ccm. of urine can be counted from time to time with the Thoma-Zeiss or Thoma-Leitz hæmatocytometer. The pus and blood may also be determined by chemical methods (Vitali test, etc.), but this is obviously less satisfactory.

III. *The Bacteriological Study of the Urine.*

The methods of making the cultures and identifying the microorganisms are those usually in vogue, and will not be dwelt upon here. Two or three loops of the shaken-up urine are plated on agar or smeared over slant agar and from the colonies growing therefrom cultures are made on the usual media, gelatin, potato, litmus milk, glucose agar, bouillon and peptone. The success or failure of any method of treatment upon the number of microorganisms may be determined by counting the number of colonies growing from one, two or three loops of urine or diluted urine upon a plate of known size.

In all cases except perhaps the acute post-operative cases, the sediment should be carefully examined for the *tubercle bacillus*, while if it is not found on such examination and there is good reason to suspect tuberculosis of the urinary tract, we should make intraperitoneal injections of some of the sediment into guinea-pigs. The tuberculin test is of slight value because of the probability of there being other foci of tuberculosis in different parts of the body.

In any case in which there is the least possibility whatsoever, the

specimen should be examined for the gonococcus, and if suspicious intracellular diplococci with the peculiar staining characteristics of the gonococcus are found, attempts should be made to grow the microorganism on special media.

INFECTIONS OF THE BLADDER.

The classification of the different varieties of cystitis is obviously dependent upon the point of view from which this classification is made. Such a classification may be anatomical (pericystitis, paracystitis, interstitial cystitis and cystitis), clinical (acute and chronic), pathological (catarrhal, suppurative, ulcerative, exudative, exfoliative, papillomatous, cystic, proliferating, emphysematous, etc.), or bacteriological (the microorganism causing the infection giving the name to the variety of cystitis).

Of course, also, a classification may be made on other grounds, whether associated with calculus, new growth, foreign body, etc. The most satisfactory classification, however, seems to us a combination of the clinical and bacteriological, thus starting with acute and chronic cystitis and subdividing these along bacteriological lines. We have also subdivided the cases of chronic cystitis into those occurring alone and those associated with pyelitis, while we have placed tuberculous infections in a separate class because of the marked differences in etiology, symptomatology and treatment between this form of cystitis, pyelitis and pyelonephritis and those caused by the other microorganisms.

Although we have no such cases to report, we must mention, in passing, that in rare instances we may have a true cystitis without any infection, where the cause is some chemical irritant as, notably, cantharides and its preparations; aniline, toluidine, naphthaline and their derivatives,[1] etc.

In making the division of our cases of cystitis into acute and chronic, we have considered those cases as acute in which the infection has been present but a short time, where there is no *real* contraction of the bladder and where there are no distinct areas of ulceration; while in the chronic cases the duration has been longer, there is practically always more or less ulceration and the bladder

[1] Leichtenstern, Deutsche medicinische Wochenschrift, 1898, No. 45, Nov. 10th.

is distinctly and usually markedly contracted. As stated before, our list includes 26 cases of acute cystitis, 31 cases of chronic cystitis, and 6 cases of tuberculous cystitis.

IV. *Cases of Acute Cystitis.*

These cases are of great interest because of the fact that heretofore no one has been able to study a series of cases of acute cystitis from before the development of the condition until a cure has been effected.

They are of especial value in definitely proving what microorganisms can give rise to cystitis, especially as regards the rôle played by the colon bacillus (bacillus coli communis) in this affection.

The exceptional advantages under which these cases have been studied arise from the fact that with two exceptions all were operative cases and consequently the urine had been carefully examined several times previous to the operation, besides which a careful history had been taken, which was of the greatest importance in ascertaining what other factors besides the introduction of the microorganisms played a part in the development of the condition.

All of these cases were women except one (26), and his case is added to the list because of its great interest bacteriologically. In all except the two cases that were not operated upon (4 and 7), the urine was examined either the day preceding or the day of the operation and found to be absolutely normal, containing neither pus-cells, red blood-cells, albumin nor bacteria.

Of course this is especially easily done in gynecological operations, as it is essential to catheterize the bladder before operating, for otherwise the distended bladder may seriously encroach upon the field of operation. Also all these 24 patients were catheterized subsequent to their operation, in some cases this being done but once or twice, in other cases catheterization being necessary for a considerable length of time; thus in one case (12) the patient was catheterized upwards of 20 times.

It is needless to say that the catheterization was done under the strictest aseptic precautions, the external urethral orifice being carefully cleansed before the introduction of the sterile glass catheter.

In this chapter we will first discuss the bacteriological findings,

and subsequently take up the probable path of infection, and the other etiological factors in the development of the cystitis.

1. *The bacteriology of these cases.*

In all these cases the microorganism causing the infection was present in pure culture and generally in very large numbers, rendering its isolation comparatively easy. In most of these cases two, and in all the rarer cases three or more cultures, were made from the urine, and in most of those cases which were continually under observation—24 in all—cultures, taken after the treatment had been carried on until the symptoms had disappeared, showed that the bacteria had entirely disappeared, although a few pus-cells continued in the urine for some time thereafter.

All the cases contained pus-cells, red blood-cells and epithelial cells, generally a larger number of the first and fewer of the red blood-cells. The number of flat bladder epithelial cells varied greatly; in some cases a great many were present, in other cases comparatively few. The bacteria found in these 26 cases were as follows:

B. coli communis, 15 times.
Staphylococcus pyogenes albus, 5 times.
Staphylococcus pyogenes aureus, 2 times.
B. pyocyaneus, 1 time.
B. typhosus, 1 time.
B. proteus vulgaris (Hauser), 1 time.
No culture made (from microscopic examination, probably B. coli communis), 1 time.

Thus in the 26 acute cases, the B. coli communis was found in 57.7 per cent (or in 61.5 per cent if the last case is included), the Staphylococcus pyogenes albus in 19.2 per cent, the Staphylococcus pyogenes aureus in 7.7 per cent, and the B. typhosus, B. pyocyaneus, and B. proteus vulgaris 3.8 per cent each.

The prevalence of the B. coli communis is extremely striking and also very important, as there are some who deny to this microorganism the ability to set up a vesical inflammation, and when they find it in the urine ascribe the cystitis to some other microorganism which subsequently was driven out by the colon bacillus. In all the cases of acute cystitis studied except one (26), the case of B. proteus vulgaris infection (the only man included in our series), the urine was acid, although the degree of the acidity varied

markedly with the variety of microorganism. The symptoms were practically the same in all cases—slight rise of temperature, frequent, burning micturition, an injected bladder (to cystoscopic examination) and pyuria.

(*a*) *B. coli communis.*—In the 15 cases in which this microorganism was found (1, 2, 3, 4, 5, 8, 11, 12, 16, 18, 19, 20, 21, 22, 23), the urine was invariably acid; the acidity seemed never to be decreased below the normal acidity, and in one case (16) it was very markedly increased, the acidity in this case being 36 (10 = normal acidity). The variations in virulence, etc., of this microorganism will be spoken of later.

(*b*) *Staphylococci.*—The staphylococci were found in 7 cases, in 5 the Staphylococcus albus (6, 7, 9, 10, 17) and in 2 the Staphylococcus aureus (15, 25). While in all these cases the urine was usually acid, it seemed generally somewhat and often distinctly less acid than normal, and in one case (25) was frequently neutral in reaction.

(*c*) *B. pyocyaneus.*—This microorganism was found in but one case (13). This case has been reported in full elsewhere,[1] and was very striking in being, as far as could be found out, the first completely proved case of a cystitis of this origin. Extremely striking was the greenish tinge of the urine which could be markedly increased by allowing the urine to remain in the thermostat for a short space of time.

(*d*) *B. typhosus.*—This case (14) has also been reported in detail elsewhere.[2] Although the typhoid bacillus has been quite frequently found to be the cause of cystitis, it has always, except perhaps in one other case,[3] been found in association with typhoid fever. In the case studied by me, the typhoid bacillus was the cause of an acute cystitis with absolutely no other symptoms whatsoever. The bacillus was identified by its growth on the usual media, by its comparison with the stock laboratory typhoid culture, and by agglutinating positively in dilutions of 1: 80 with the blood of a patient who at that time was suffering from a typical attack of typhoid fever. The cause of the localization of this micro-

[1] Maryland Medical Journal, May, 1900.

[2] Medical Record, 1900, March 10.

[3] Houston, British Medical Journal, 1899, I., p. 78.

organism in the bladder in this case was difficult to determine, unless it were for the fact that 35 years previously the patient had had typhoid fever and she was, therefore, probably less susceptible to a general infection with the B. typhosus.

(*e*) *B. proteus vulgaris.*—Although this case is one of a man, it is included here because it is the only case of acute cystitis in my series in which the urine was alkaline. In this case the urine was strongly ammoniacal and the sediment contained enormous numbers of triple phosphate and ammonium urate crystals, besides pus, blood and bladder epithelial cells.

2. *Time of the development of the symptoms.*

The length of time after the operation before the development of symptoms of cystitis is of some interest in perhaps throwing light upon the virulence of the different microorganisms and the varying degrees of resistance of the different patients. In the case of the colon bacillus, this varies from the 4th to the 20th day, the average being 11.7 days; in the case of the white staphylococcus, from the 9th to the 20th (average 14.5); the yellow staphylococcus, from the 5th to the 7th day (average 6); while in the cases of pyocyaneus, typhosus and proteus infections the times were 9, 9 and 3 days respectively.

Although nothing definite can be deduced from this because of the multiplicity of factors involved, one is at once struck by the wide variability of the colon bacillus and by the comparatively rapid development in the case of the B. proteus, the Staphylococcus aureus and some specimens of the B. coli communis, suggesting that these were the most virulent infecting microorganisms.

3. *Mode of entrance of the bacteria into the bladder.*

The possible modes of entrance of bacteria into the bladder are numerous; thus we may have invasion through the urethra, through either ureter, through some pathological opening between the bladder and some other organ as the vagina or intestine, or from some adjacent abscess cavity. Besides these modes of entrance we must also consider the possibility of the infection being carried from various parts of the body by the blood or lymph currents, and perhaps also a direct passage of microorganisms from the rectum to the bladder through the recto-vesical tissues.

In considering these cases of acute cystitis, however, the only two probable means are, it seems to us, infection through the

urethra, and infection from the rectum or some focus of infection either by means of the blood or lymph currents or by direct transmission. Of these two, the former—infection through the urethra—is certainly the more common, and in the large majority of cases this is undoubtedly brought about by catheterization.

It is of interest here to consider the bacterial flora of the normal female urethra and vestibule of the vagina. Melchior examined the urethras of 6 healthy women and in all found various bacteria, the Staphylococcus liquefaciens urethræ in 3, the Cocco-bacillus liquefaciens urethræ in 1, the B. urethræ non-liquefaciens in 2, the Pseudogonococcus, Diplococcus candidus urethræ, Sarcina urethræ and Streptococcus liquefaciens urethræ in 1 each. Of these the staphylococcus and streptococcus can produce cystitis under the proper conditions. Savor found the colon bacillus in 4 of 12 healthy women's urethras; Gawrowsky found the colon bacillus twice, the Streptococcus pyogenes 3 times and the Staphylococcus pyogenes 8 times in the examination of the urethras of 62 healthy women. In the vulvæ of healthy women, Melchior found the colon bacillus in half the cases he examined; Bouchard and Charrin also found this microorganism frequently in this location; Schenck and Austerlitz, however, found the colon bacillus in only 2 of the 60 urethras examined.

It will thus be seen that in all probability in a large number of cases the colon bacillus is to be found in the vestibule of the vagina, although to a decidedly less extent in the urethra, while among other microorganisms various staphylococci are to be found in these locations. When we consider in the first place the proximity of the urethral to the anal opening, and in the second place the fact that in a number of these cases there was also a considerable leucorrheal discharge, the possibility of infection from this source is seen to be very great, especially as catheterization was practiced frequently, although under the strictest precautions. Thus in the great majority of cases it is probable that the infection is brought about by the introduction of germs from the vestibule of the vagina or the urethra by catheter; under our present aseptic and antiseptic methods the introduction of pathogenic germs from the air can be ignored.

In a few cases, however, catheterization was not performed, and in these we must consider other methods of infection. Cases 3,

4 and 7 are of especial interest in this connection; in Case 3, although catheterization had been performed for the first 3 days after the operation, the cystitis did not arise until the forty-eighth day; it it therefore highly probable that the germs were not introduced by the catheter, while in cases 4 and 7, catheterization had never been performed. In Case 4 the cystitis came shortly after giving birth to a child and was preceded by a profuse uterine discharge. The infection therefore in this case was probably an ascending urethral infection, the congestion of all the tissues rendering the bladder peculiarly liable to infection; in Case 7 the cystitis appeared spontaneously, without any apparent cause except that the patient was very anemic and poorly nourished. In this case, as in Case 3, there is certainly a possibility that the infection came from the rectum, although, of course, it might have been an ascending urethral infection.

In this connection it is of interest to note that Carlier[1] reports 2 cases of diarrhea in men followed by attacks of acute cystitis, and that Van Calcar[2] comes to the conclusion from a long and carefully performed series of experiments upon rabbits, that in a considerable number of cases of infectious cystitis the infection comes directly from the digestive tract, probably by the subperitoneal path.

It certainly is difficult to explain some of the cases of cystitis that arise spontaneously upon any other basis, and we must consider this as a possible mode of infection in all cases.

4. *Other etiological factors in the development of cystitis.*

One is at once struck, on considering the microorganisms that were found in these cases of acute cystitis, by the fact that many of them, the colon bacillus and the white staphylococcus for instance, are bacteria of usually a low order of pathogenicity. One is therefore impelled to inquire carefully into the individual cases to see if there are not other factors at work which, so to speak, prepare the bladder for the reception of these germs and render it susceptible to their usually low pathogenic powers.

In *all* our cases, one or more factors are found tending to lower the resistance of the bladder to infection. These factors may be briefly enumerated as follows:

[1] La Médecine moderne, 1898, Oct. 22.

[2] Nederl. Tijdschrift voor Geneeskunde, 1899, II, p. 1188

(*a*) The patient has a high grade of anemia, as seen in cases 3, 7, 8 (hemoglobin = 57%), 9 (hemoglobin = 25%), 14 (hemoglobin = 51%), 15 (hemoglobin = 51%), 17 (hemoglobin = 33%), 18, 19, 20 (hemoglobin = 68%), 23 (hemoglobin = 50%) and 25. This naturally markedly reduces the general power of the patient to resist infection and is generally associated with malnutrition.

(*b*) Constant pressure on the bladder by new growths, other organs, etc., making it much congested, as seen in cases 8, 9, 10, 11, 14, 15, 16, 17, 20 and 24. This was evidenced by the fact that previous to the operation the pressure of these large tumors, mostly uterine myomata, upon the bladder, produced in that latter organ some of the symptoms of cystitis—frequent burning micturition, due undoubtedly to the congestion induced in that organ by the pressure. The urine, however, previous to operation was in all cases negative.

(*c*) The relaxation of the vaginal outlet causing some sagging of the bladder and the consequent congestion of that organ, as seen in Case 12.

(*d*) The trauma of the bladder inevitable to any operation for the removal of a large tumor or for various forms of pelvic peritonitis or appendicitis when adhesions have formed about the bladder and have to be separated. This was the case in the great majority of our cases and was undoubtedly a most potent factor in the development of the infection. Almost all the operations performed were of serious nature, and in the great majority many adhesions had formed about the bladder and had to be separated, as seen in cases 1, 2, 3, 5, 8, 9, 10, 11, 13, 14, 15, 16, 17, 20, 21, 24.

(*e*) The trauma and congestion of the bladder incidental to childbirth, as seen in cases 4, 22 and 23. In Case 4 this was associated with a profuse uterine discharge, in cases 22 and 23 the delivery was instrumental and catheterization had to be performed several times.

(*f*) Catheterization with poor technique. This is seen in Case 26, a man operated upon elsewhere for appendicitis 3 weeks before being seen by us and catheterized many times by an orderly whose aseptic precautions were very inefficient. To this must be added the possible trauma from the hard end of the catheter.

(*g*) As other causes we must consider the direct extension from a large appendicular abscess as seen in Case 25, where the bladder

infection was due to the Staphylococcus pyogenes aureus and from other adjacent foci of infection.

From a careful consideration of these contributory causes one is compelled to admit that they play an extremely important rôle in the etiology of cystitis. Usually several of these factors are operative in any special case, but under rare conditions the vitality of the patient is so low, or the bladder is in such poor condition, due to the pressure of tumors or of other organs, that infection will arise spontaneously without catheterization, this being especially likely to occur in case of a purulent uterine or vaginal discharge, or if the patient exhibits some form of intestinal disturbance. It is, however, the *microorganism* that sets up the infection, although from the fact that so few patients, except such as those whose vitality is low or whose bladders have been rendered susceptible to infection by trauma, congestion due to pressure, adhesions, lack of support, etc., develop cystitis, it is seen how large a part these contributory causes play. This agrees with the experimental work of Melchior, Rovsing and others, who found that in the case of the majority of microorganisms, cultures could be injected into the bladder of healthy animals without doing any harm, while if the bladder was made to undergo trauma or congestion, or the urethra was ligated for several hours, a typical attack of cystitis was brought about. In the case of the urea-splitting microorganisms (Bacillus proteus), these contributory factors are apparently not necessary, as the irritation of the ammoniacal urine seems in itself sufficient to bring about the conditions necessary for the development of a cystitis.

Cases 15 and 26 are of especial interest, for in these the bladder infection was followed shortly by an ascending infection to the kidney and the development of a pyelitis.

5. *Bacteriuria.*

We have met with no condition of bacteriuria proper, *i. e.* where the urine becomes infected, but there is no lesion of the urinary tract, and thus the urine contains myriads of bacteria but no pus-cells.

The B. coli communis is usually the microorganism found, as especially insisted upon by Rovsing, but Roberts and Hallé have described a bacteriuria due to micrococci, and Hogge to streptococci and staphylococci.

The bacteriuria may apparently be either renal or vesical in origin.

Two of our cases (17 and 20) approach very closely to cases of bacteriuria in that they showed comparatively few pus-cells but enormous numbers of bacteria, the Staphylococcus pyogenes albus in the former case, the B. coli communis in the latter. Rovsing describes a variety of bacteriuria where a few pus-cells are to be found in the urine, but it appears to us that this cannot in reality be called a pure bacteriuria; for, as in our 2 cases, a *marked* infection of the urine is associated with a *mild* infection of the bladder, the former shown by the enormous numbers of bacteria, the latter by the small numbers of pus-cells. It is highly probable that all degrees of infection could be found by careful study, from the pure vesical bacteriuria to the highest grade of cystitis.

Before proceeding to the next chapter, one should note that in 2 cases (49 and 50), pyuria was present but no microorganisms were found (either by microscopical examination of the sediment, transplantation of the urine or the various media or by the special staining for the tubercle bacillus). It was thought probable that in these cases the infection had died out of itself, as undoubtedly sometimes happens, although it is impossible to rule out tuberculosis absolutely.

V. *Cases of Chronic Cystitis (non-tuberculous).*

These cases have been considered separately from the cases of acute cystitis to see if there was any marked variation in the proportionate part played by the various microorganisms causing the trouble.

Thirty-one cases of this nature have been studied bacteriologically. The duration of the condition varied between 2 months and 20 years, and in the great majority of cases was several years. The symptoms varied markedly according to the extent of the infection; in some cases they were comparatively slight, while in others they were such as to render life practically unbearable, there being pain, tenesmus, urination so frequent that none of the duties of life could be attended to, and marked ulceration and contraction of the bladder, in one case the bladder holding but 15 ccm.

In fact, in the more severe type of cases the condition was so

deplorable that the patient was willing to undergo any pain or any discomfort that furnished the slightest chance of relief.

The cases of chronic cystitis have in turn been subdivided into those occurring alone and those associated with pyelitis.

From a consideration of the latter series of cases, 7 in all, we may conclude that in cases where the pyelitis precedes the cystitis, the cystitis is likely to be rather mild in character; while in some of the cases in which the cystitis precedes the pyelitis, after a certain length of time the vesical symptoms may become minimal, the renal symptoms and renal infection still remaining marked.

Of these cases of associated cystitis and pyelitis, in 3 (55, 56, 57) the pyelitis preceded the cystitis by a considerable length of time, and in all 3 the cystitis symptoms were very mild. Whether this is due to a certain tolerance of the organism as a whole towards the infection after it has remained localized for a considerable time in the kidneys it is impossible to say.

Of the other 4 cases (51, 52, 53, 54), those in which the cystitis preceded the pyelitis, the cystitis arising 1 year, 4 years, 5 years and 8 months respectively before the patient came under observation, and the pyelitis appearing a few weeks, 2 years, 4 years, and 1 month respectively after the appearance of the cystitis, in 3 (51, 52, 54) the symptoms of cystitis had become gradually less after the development of the pyelitis, and when the patient came under observation were very mild indeed; in 1 (53), however, the symptoms of cystitis were present in a maximum degree and the bladder showed most marked ulceration and contraction.

In all the cases of associated cystitis and pyelitis except this one last mentioned, the cystoscopic examination showed but a slight localized inflammation, usually about the affected ureteral orifice or of the trigonum or both.

The cystoscopic examination of the cases of chronic cystitis occurring alone varied from a moderate condition of ulceration and contraction to pathological changes of the most severe type.

1. *Bacteriological findings in the cases of chronic cystitis.*

In the 24 cases of chronic cystitis occurring alone, the following microorganisms were found:

B. coli communis, 11 times.

Staphylococcus pyogenes aureus, 3 times.

Staphylococcus pyogenes albus, 2 times.

B. coli communis (with tubercle bacillus), 1 time.

Unidentified (possibly a variety of the B. coli), 1 time.

Cultures not made, 2 times.

Pyuria sterile, 2 times.

A staphylococcus albus (which decomposed urea, was pyogenic, but either did not liquefy gelatine or did so extremely slowly), 2 times.

In all these cases except the last 2 (cases of the slowly-liquefying white staphylococcus), the urine was usually acid, although occasionally neutral and, exceptionally, slightly alkaline in the case of the other staphylococci.

In the 2 cases of the slowly-liquefying white staphylococcus, the urine was always either alkaline or ammoniacal.

In the 7 cases of associated cystitis and pyelitis, the micro-organisms found were:

B. coli communis, 4 times.

B. proteus vulgaris, 1 time.

Slowly-liquefying staphylococcus albus, 2 times.

In the case of the B. coli, the urine was always acid; in the other 3 cases the urine was sometimes acid, sometimes neutral and sometimes alkaline (in these 3 latter cases the cystitis was slight, the pyelitis marked).

Thus in the whole series of cases of chronic cystitis, the B. coli communis was met with in 16 of the 29 cases in which a bacteriological examination was made, or in 55.2%; the Staphylococcus pyogenes aureus in 3, or 10.3%; the Staphylococcus pyogenes albus in 2, or 6.9%; the slowly-liquefying, urea-decomposing white staphylococcus in 4, or 13.8%; the B. proteus vulgaris in 1, or 3.4%.

Of the 31 cases, the urine from the bladder was acid in 26 (occasionally neutral in some of the staphylococci cases), alkaline or ammoniacal in 5 (occasionally acid or neutral where the pyelitis is marked, the cystitis slight).

(*a*) *B. coli communis.*—This was present alone in cases 27, 28, 33, 34, 36, 37, 39, 40, 41, 43, 44, 51, 53, 54, 57, and associated with the Tubercle bacillus in Case 46. In Case 31 an unidentified bacillus was found, which resembled the Colon bacillus in all respects except that it did not form gas in glucose agar nor indol in peptone solution. The most marked variations in virulence were seen in the case of the colon bacillus, thus in cases 40 and 53 its

virulence was quite as marked as in the case of any of the most virulent pyogenic microorganisms except perhaps the streptococcus. In all cases the urine was distinctly acid, usually markedly so.

(*b*) *Staphylococcus pyogenes albus and aureus.*—The ordinary white staphylococcus was found in cases 32 and 44, and the orange staphylococcus in cases 29, 35 and 38. In these cases the acidity of the urine was decreased, and on some occasions the urine was neutral, and exceptionally slightly alkaline in the case of the Staphylococcus aureus.

(*c*) *Non- or slowly-liquefying, urea-decomposing white staphylococcus.*—In 4 cases (30, 42, 55, 56) a microorganism was found with most of the cultural peculiarities of the usual Staphylococcus pyogenes albus, except that it either did not liquefy gelatine or liquefied it extremely slowly, and also its growth on agar was perhaps a little more waxy than usually noted in the case of the Staphylococcus albus.

Its most striking characteristic, however, was its marked power to decompose urea, rendering the urine rapidly alkaline or ammoniacal.

The only difference between this microorganism and Melchior's Staphylococcus ureæ liquefaciens is that in the latter the liquefaction of the gelatin was noted usually by the end of one week's time, while in the case of our microorganism it was several weeks before liquefaction set in in some cases, while in other cases there was no sign of liquefaction at the end of a month's time. In our cases, however, the infection had been present for a long period of time, 14 and 15 years in 2 of the cases, and 3 years in a third, and it is possible that the power of the microorganism to liquefy gelatine had diminished somewhat owing to its long habitat in the urinary tract. This microorganism also resembles markedly the Staphylococcus epidermididis albus and the Staphylococcus cereus.

(*d*) *Bacillus proteus vulgaris.*—This was found in but one case (52), a case of cystitis followed by pyelitis, the latter condition subsequently dominating the picture.

2. *Modes of entrance of the infection.*

The various modes of entrance of the infection mentioned under acute cystitis find their representatives here, besides which several new and interesting modes of entrance are met with. The commonest of these modes of entrance is through the urethra by catheter,

used either after an operation, during pregnancy and the puerperium or in connection with the cystoscope for examining and treating the bladder for what was in many cases undoubtedly simply a neurosis of that organ; undoubtedly in this last group of cases the infection did not *precede* but *succeeded* the treatment for supposed disease of the bladder. Besides this, the commonest mode of infection, we must again insist upon the possibility of infection from the intestinal canal either by direct invasion or by metastasis by means of the blood and lymph currents in those cases of weak anemic women where the infection arose without any apparent cause and without catheterization. It is interesting to note that this occurred several times at the time of the menopause, or directly after it. Other rarer modes of infection are, from pelvic inflammatory trouble (32), through a suprapubic incision (made in tuberculosis of the bladder) as seen in Case 46, through a vesico-vaginal fistula (48), and from the kidneys in the shape of a descending ureteral infection (55, 56, 57).

An ascending urethral infection without the use of the catheter must also be considered as one of the possibilities.

3. *Other factors in the etiology of the condition.*

Although, as stated before, it is essential that microorganisms reach the bladder by some one of the various routes mentioned above, in order that cystitis should arise, it is essential that other factors are present before this infection will really take place.

The factors exemplified in these cases as predisposing conditions and which are practically the same as in the cases of acute cystitis, are (*a*) *trauma* to the bladder, incurred during operation, especially gynecological operations; during catheterization; after mechanical injury to the bladder, as in cases 29 and 49; during childbirth and after instrumental examination of the bladder. Especially pathetic are those cases in which the last-mentioned factor plays a part; in the majority of these the patient is in a nervous, depleted condition and develops slight vesical symptoms, some burning and frequency of micturition, as is frequently seen in neurasthenia and various neuroses, although the urine shows absolutely no signs of any infection; the doctor examines, treats, irrigates the bladder and infection is set up. This was undoubtedly the cause in cases 31, 33, 40 and 53; two of these cases (40 and 53) were types of the most severe form of chronic cystitis. Also there must be added those cases of

extremely poor technique in catheterization, where the trauma to the bladder wall and the introduction of the microorganisms are brought about by the faulty methods of the catheterizer (cases 42 and 45).

(*b*) *Congestion* due to the relaxation of the vaginal outlet, the pressure of other organs or of tumors upon the bladder, the presence of adhesions, and pregnancy must be considered as especially predisposing causes of the development of cystitis. *Retention* of urine is also found in some of these conditions and is an important factor.

(*c*) *Operations upon the urethra*, removal of a carbuncle (38, 39) or removal of a portion of the urethral mucous membrane (35) must be considered as predisposing causes, and also *operations* on the bladder itself (46), although in reality these fall under the head of trauma.

(*d*) Anything tending to lower the general condition of the patient seems to render infection more probable, as anemia, malnutrition, acute infectious diseases (influenza in Case 51), cold (34), the changes incident to the menopause (28, 37), etc. The cases where cystitis developed with no other reason than a general condition of anemia and malnutrition are especially interesting (28, 37, 44, 52, 54), in that in these cases the infection must have arisen by direct ascent of the microorganisms up the urethra, or from the intestinal tract.

As in the cases of acute cystitis, so here again one is compelled to assign quite as important a rôle to these contributory factors in the development of cystitis as to the microorganisms themselves, although the latter are the *absolutely essential factors.*

VI. *Tuberculous Cystitis.*

Six cases of tuberculous cystitis were met with in our series. In one case, and possibly in another as well, the cystitis occurred alone, while in the other four the cystitis was associated with pyelitis or pyelonephritis.

Five of the cases were distinctly chronic, the symptoms of cystitis having been present for from one to several years. In all of these cases except one, the bladder showed marked pathological changes, contraction, hyperemia, ulceration, thickening, often even adhesions

to other pelvic organs and invariably marked ureteral thickening of the affected side if there was a pyelitis associated with the cystitis. In the exception mentioned above, *i. e.* the case where the pathological changes in the bladder were slight (62), the bladder symptoms seemed to have markedly improved after the establishment of the pyelitis.

In the other 5 cases the symptoms of a severe cystitis were marked, pain, tenesmus, frequent micturition, hematuria sometimes marked, usually however less than the pyuria, which was always present in a high degree, and inability of the bladder to hold a large quantity of urine. In addition to this, the constitutional symptoms were much more marked than in the non-tuberculous cases of chronic cystitis; fever, night-sweats, etc., were frequently noted, as also a gradual impairment of health, strength and weight.

In one case (63), the condition was comparatively acute, the symptoms of cystitis appearing but 3 months before the patient came under our observation, and ulceration and contraction of the bladder were slight.

These cases of tuberculous cystitis have been considered under a separate heading because in the first place their general etiology, course and symptomatology are so different from those of other cases of chronic cystitis, and in the second place, the rationale of their successful treatment is based upon entirely different grounds.

In all these cases the urine was acid, generally more acid than normal urine, and in most of the cases one was struck with the rather large numbers of red blood-cells revealed by the microscope, in comparison with the findings in ordinary cases of chronic cystitis.

1. *The bacteriological findings* in these 6 cases were as follows: In all 6 the Tubercle bacillus was found, in some cases (as in Case 61) in comparatively large numbers, in other cases (as in Case 59) in small number, and only found after long and careful search. Speaking generally the *Tubercle bacilli* were present in small number and it demanded considerable patience to find them.

In all cases except one (58), cultures from the urine made on the ordinary media were absolutely negative; in Case 58, at first the Tubercle bacillus was found in pure culture, but after the performing of a suprapubic cystotomy, *B. coli communis* was also found.

Obviously it was unnecessary to eliminate the smegma bacillus and the bacillus of syphilis (?) in these examinations, as the bacilli

were not sought for in the voided specimens of urine, but in those obtained by catheter under the most careful aseptic precautions.

2. *The mode of entrance of the Tubercle bacilli* is very interesting. If one can place any reliance upon symptoms, in 5 cases, and perhaps in all 6, the bladder was affected first. Certainly in the 4 cases of associated pyelitis and cystitis the symptoms of cystitis were marked a considerable time before the patient noted any renal symptoms whatsoever.

The exact mode of entrance of the bacilli was difficult to exactly determine, in the great majority of cases it was probably by means of the blood or lymph currents from some tuberculous focus in some other portion of the body. One cannot rule out, however, the possibility of an ascending urethral infection, although there is no evidence of such in any of our cases. In one case (59) there is a possibility of the tuberculous cystitis being secondary to a tuberculous pyelonephritis. In no case except in Case 59 was there discovered the tuberculous lesion whence the affection arose; in Case 59 the lungs seemed affected at the time of a previous examination, but in the other 5 cases there were no pulmonary symptoms and the examination of the lungs was absolutely negative.

In these cases the original source of infection was probably some tuberculous lymph gland, mediastinal or mesenteric.

In most of the cases the symptoms of pyelitis appeared from a month to a few months after the symptoms of cystitis; but in Case 62, that of a strong, hearty woman, 17 months elapsed between the first appearance of symptoms of cystitis and of pyelitis.

3. *Other etiological factors* are more difficult to determine in the tuberculous than in the other cases; in none of the cases did catheterization or trauma play a part in the development of the condition.

(*a*) *Heredity* seems to have played a part only in one case (59); in all the others the family history was good in this connection. In Case 59 a pulmonary lesion, probably tuberculous, was also present.

(*b*) Weakness, anemia and malnutrition seem to have played a distinct rôle in some of the cases, notably cases 61 and 63, where the patients were in poor physical condition for some time before the development of the trouble. Of course this might have been due to the presence of some tuberculous lesion elsewhere.

In some cases the onset was gradual and insidious, as in cases 58 and 60; the condition had lasted for a long while, increasing in severity, although of a distinctly chronic nature from the first; in other cases the onset resembled that of an ordinary acute cystitis as in cases 61, 62 and 63, although in cases 61 and 63 the symptoms gradually increased from those of the acute onset.

In Case 62, a strong, healthy woman, the cystitis became gradually better as time went on, so that the symptoms of cystitis were very slight when the patient came under our observation; a spontaneous cure would probably have been established were it not for the associated pyelonephritis.

Thus we see that tuberculous cystitis presents a many-sided picture; its onset may be very acute, subacute or insidious, with the features of chronicity from the start; its course may be slow or rapid; thus in Case 61, of only 2 years' duration, the pathological changes in the bladder were more marked than in cases 58 and 60, where the lesion had been present for many years; there may be a distinct tendency of the condition to heal itself, as in Case 62, where if the kidney had not become secondarily affected, a spontaneous cure would have probably taken place.

Probably in the determination of the conditions, which shall exist in the individual case, the number and virulence of the microorganisms introduced, the resistance of the patient, her general physical condition, her mode of life and her family history are important factors.

In some cases the symptoms were comparatively slight—pyuria, frequent micturition, slight pain; in others of the most severe type and with the local symptoms were associated marked constitutional symptoms.

Cases 58 and 63 were in girls between 20 and 30 years of age; the others were in women between 40 and 50; of these 4 latter cases, all except one (62) were married.

VII. *Cases with Symptoms of Cystitis but No Infection.*

It is, of course, a well-known fact that certain symptoms of cystitis occur in a mild degree in a variety of other conditions.

Thus, increased frequency of micturition, either alone or associated with slightly burning, somewhat painful urination is noted after the ingestion of a large list of drugs such as copaiba, cubebs,

camphor, cantharides in small doses (large doses bringing about a true cystitis), etc., etc., and also during the course of many fevers, due perhaps to the noxious substances being eliminated, perhaps to the concentration of the urine. It is also met with in various neurotic, neurasthenic and hysterical conditions, associated with a urine of very low specific gravity. These cases, however, should give us no trouble in diagnosis as the cause is usually easily determined by a casual survey of the case, although in some cases, as during the course of the infectious fevers, this increased frequency associated with slight pain is sometimes followed by a true cystitis, the inevitable congestion of the bladder rendering infection possible if the microorganisms are introduced.

There is, however, a certain class of cases whose symptoms simulate cystitis much more closely, so closely in fact that in many cases physicians themselves have been deceived thereby and have given the patient local treatment (irrigations, etc.), which in its turn produced a true cystitis due to congestion or trauma of the bladder induced by the treatment and the introduction of microorganisms, often leading to deplorable results, as in cases 40 and 53. Thus in these cases treatment not only does no good, but it may, and frequently does, do positive harm.

It is for this reason especially that we insist on the absolute necessity of studying the urine bacteriologically in every case, even in those where the urine contains pus-cells, before inaugurating any form of topical treatment.

I have subdivided this class of cases into—

1. Those where the symptoms are due to hyperacidity of the urine.

2. Those where the symptoms are due to other causes.

1. *Hyperacidity of the urine*, as far as I know, has never been described as a cause of symptoms which may quite easily be mistaken for those of cystitis, and yet undoubtedly this is a cause, and probably a frequent one, if one can judge from our series. I was struck by the fact, in several of the cases which we saw, who complained of frequent, painful, burning micturition, often of a high grade, whose urine contained pus-cells, although in small amount and yet was sterile, showing bacteria neither by microscopical examination of the sediment nor by transplantation on the various media, that the urine was more acid than usual, as it colored

the blue litmus paper used in testing the reaction a brighter red than usual.

It was therefore thought, as no other cause could be determined for the symptoms presented, that the irritation due to an excess of acid or of acid salts in the urine might be at the bottom of this condition. Quantitative determinations of the total acidity were therefore made by titration of 10 ccm. of the urine (immediately after it is withdrawn from the bladder) with one-tenth normal sodium hydroxide solution, using phenolphthalein as the indicator, this method being used in preference to the more complex (and somewhat more exact) method of determining the total acidity by estimation of the acid phosphates present, because of its greater practicability.

A series of normal cases was taken to determine the average quantity of acid present, and this average or normal amount we have designated for convenience as 10.

Since this work has been started we have met with 9 cases in all, where the symptoms could be directly referred to an increase of acidity in the urine (cases 64 to 72 inclusive). All these cases presented symptoms of frequent, painful, burning micturition, in some not so marked as in others, but in the latter of such a high degree as to absolutely simulate a true cystitis.

The urine always contained pus-cells, usually in very small number; a very few red blood-cells and some bladder epithelial cells; while a cystoscopic examination always revealed a more or less reddened trigonum ("trigonitis"), in some cases the injection of this portion of the bladder being of the maximum degree; the upper portion of the urethra is also often injected. Cultures of the urine were always sterile.

The acidity of the urine in these cases was respectively 27.5, 30, 30, 31, 30, 49, 21, 31, 29; *i. e.* in all these cases the acidity was at least twice, and in one case nearly five times, as great as normal.

In trying to discover the *cause* of this hyperacidity, one was at once struck by the fact that all the cases exhibited neurasthenical, neurotic or hysterical manifestations, in most of the cases in a marked degree, and it was therefore regarded as highly probable that this hyperacidity was of neuropathic origin (Case 70 perhaps does not belong to this group, as there were other factors probably involved). This is also suggested by the fact that practically all

these cases had noted that their bladder symptoms became much worse if they were under severe mental or nervous strain, and by the result of treatment.

The *treatment* was designed both to counteract the hyperacidity and to improve as far as possible the general condition and "tone" of the patient.

For the first purpose, alkalies were administered by mouth in sufficient amount to render the urine neutral or alkaline; for the second, the patient was given food between meals, rest, sunshine, iron if the hemoglobin was low, strychnia in most cases, while in some of the cases a veritable rest cure, sometimes associated with cold packs and generally with massage was found to be necessary.

In the 4 cases in which this full treatment was carefully carried out, the symptoms rapidly disappeared, although of course it was highly probable that they would reappear if the patient subsequently relapsed into her previous neurotic, hysterical or neurasthenical condition.

This occurred in one case (66), who was entirely free from all symptoms for 6 months; after overexertion and too great nervous strain the symptoms reappeared, and were again driven away by the same treatment as before.

All the patients were young women, and I have thought that, in a certain way, the condition was somewhat analogous to gastric hyperchlorhydria. This condition has been dwelt upon at some length; in the first place because, as far as I know, although of course vesical irritability has been described before in neurotic subjects, urinary hyperacidity has not been considered in this connection, and, in the second place, because of the absolute necessity for recognizing this condition and not confusing it with a true cystitis.

One has but to look through our list of cases of chronic cystitis to see how, in a number of them, a condition which was undoubtedly but urinary hyperacidity in a young, nervous girl was misinterpreted, and treated as if it were a case of cystitis, with the unhappy result that by the treatment itself an infection of the bladder was set up, the congestion of the bladder seen in urinary hyperacidity probably rendering infection especially easy.

2. Those cases where the symptoms are due to other causes are frequently met with; *i. e.* cases of frequent, sometimes painful

urination, frequently with a few pus or blood-cells in the urine, often some congestion of some portion of the bladder, but where there is absolutely no infection whatsoever. These symptoms find their explanation in the diseased condition of some other of the organs or tissues of the pelvis. Of course numbers of cases of this kind are to be met with in gynecological work. Such causes in our series have been (*a*) relaxation of the vaginal outlet (73, 75); (*b*) retroflexed uterus (75, 78, and also 12); (*c*) pelvic inflammatory disease with many adhesions between the pelvic organs and the bladder (74); (*d*) large pelvic neoplasms such as uterine myomata or ovarian cysts, pressing upon the bladder and often adherent to it (80, and also cases 9, 10, 11, 16, 20, 24); (*e*) mucous polyps protruding from the vagina (77); (*f*) varicosity of the vesical veins, occasionally causing hematuria and frequent micturition after exertion or without apparent cause (79).

In these cases the diagnosis is of course easy and the correctness of this diagnosis is shown by the fact that if the pelvic condition is corrected, the tumor removed, the adhesions separated, the relaxed outlet lifted up, the polyp removed, the retroflxed uterus suspended as the case may be, the vesical symptoms shortly disappear. It is also interesting to note that in those cases in which infection is already present, as in Case 47, the treatment of the cystitis may be remarkably facilitated by correcting the pelvic trouble, this being in the case mentioned a markedly relaxed vaginal outlet.

It will thus be seen that a careful pelvic examination is also absolutely necessary in determining the cause of this symptom-complex, suggestive of cystitis, but without infection.

Pyelitis and Pyelonephritis.

The bacteriological study of the infections of the kidney is much more difficult than in the case of bladder infections, and the results have hitherto been much less satisfactory, due to the fact that in practically all the cases the diagnosis has been determined from the symptoms alone and the bacteriological studies have been made upon the urine obtained from the bladder, and not *directly* from the *kidney*.

Of course, as we stated before, a diagnosis of pyelitis or pyelo-

nephritis can be made in the great majority of cases from the symptom-complex presented, by the examination of the urine, especially as regards the relation between the albuminuria and the pyuria (and hematuria), the crenation of the pus-cells and the red blood-cells and the presence of epithelial cells from the pelvis of the kidney, and finally by a careful cystoscopic examination, noting especially the condition of the vesical mucous membrane surrounding the ureteral orifices and the condition of the urine flowing from each; in some cases it is even advisable to use some one of the various urine separators that have been advocated.

Our series of cases, however, differs from any of the others in that the urine was obtained directly from the kidney by means of ureteral catheterization, and our bacteriological and microscopical studies were made from the urine thus obtained.

We were able, therefore, not only to study the suspected side, but, by obtaining a catheterized specimen from the outer kidney, to compare the two, to determine whether infection was or was not present in the apparently normal side and to determine quantitatively the amount of urine and the quantity of urea excreted by each kidney separately.

These latter considerations are of immense importance in coming to a decision regarding the propriety of performing nephrectomy.

Twenty cases of pyelitis and pyelonephritis have been studied by us, comprising 2 of acute pyelitis and pyelonephritis, 12 of chronic, non-tuberculous pyelitis and pyelonephritis, and 6 of tuberculous pyelitis and pyelonephritis.

VIII. *Acute Pyelitis and Pyelonephritis.*

But 2 cases of acute pyelitis have been met with by us; in one the *B. coli communis* was the cause, in the other the *B. proteus vulgaris* (the latter case is that of a man but is added because of its interest). In the case of the B. coli infection the urine was acid, while in the case of the proteus infection it was alkaline or ammoniacal.

In both cases the pyelitis was preceded by a cystitis; thus the mode of entrance of the infection into the kidney was by ascent of the ureter from the infected bladder.

In the colon infection the woman was extremely weak and

anemic, and the cystitis, which developed on the 11th day after the operation (a simple nephropexy) was followed in a few days by the infection of the kidney that had been suspended. The urine from the other kidney was normal. It was of interest that in the ascending infection from the bladder only the kidney that had undergone a certain amount of trauma and handling at the preceding operation should become infected.

In the case of the infection with the B. proteus, the entrance of the infection into the bladder was undoubtedly brought about by extremely poor technique when the patient was catheterized. The urine was intensely ammoniacal and the sediment consisted of a mass of triple phosphate and ammonium urate crystals, with many pus-cells and some red blood and epithelial cells.

In both cases the urine showed considerable albumin.

In the case of the proteus infection, the virulence of the micro-organism was definitely shown by the rapidity with which both the infection of the bladder and that of the kidney was set up, and by the severity of the infection in either case.

IX. *Chronic Pyelitis and Pyelonephritis (non-tuberculous).*

In all, 12 cases of this condition have been studied, in 4 of which the pyelitis has been present alone, in 8 in association with cystitis.

In each of these cases both ureters were catheterized, although the ureteral catheter was inserted but a short distance up the ureter of the side which did not appear to be affected, and this only after the operator had thoroughly washed out the bladder and swabbed off the mucosa contiguous to the ureteral orifice with a solution of nitrate of silver.

From this double catheterization it was found that in 11 of the 12 cases (all except Case 88), only one kidney was affected, the urine from the other kidney being absolutely normal. It is of especial interest to compare the urine from the two kidneys, not only from a bacteriological, but also from a chemical point of view; thus, speaking generally, while the urine from the normal side would have all the characteristics of normal urine, the urine from the affected side would usually be of much lower specific gravity, contain much less urea, although usually a greater quantity of

urine would flow from the affected side than from the normal side in a given time (causing the well-recognized polyuria). Especially striking were those cases where the microorganism causing the pyelitis was of that class that split up the urea, for in those cases the urine from the affected kidney would be alkaline, and from the normal kidney acid, while the reaction of the urine obtained from the bladder would be either acid, neutral or alkaline, depending in the first place upon the relative quantities voided by each kidney and the total alkalinity and acidity of each, and in the second place upon whether the bladder also was infected with the same microorganism; if the cystitis was of a high grade the urine of course would be constantly alkaline or ammoniacal in these latter cases. The symptoms were very variable; in some cases they were practically nil, in others the onset was insidious and the pain never acute; in still others the onset was sudden, with acute pain, fever, etc., followed by a reappearance of these symptoms, at varying intervals, the symptoms in the intervening periods being either wanting altogether or consisting of more or less constant, dull, aching pain. As we shall see later, the character of these symptoms seems to depend largely upon the mode of infection, and upon whether or not stone is associated with the infection.

In all cases except one (87) where the pyuria was very slight, there was considerable albumin present in the urine; the pus-cells and the red blood-cells (usually few in number) often were crenated, and renal epithelial cells were usually found.

1. *Bacteriology.*

The bacteria found in these 12 cases were as follows:

B. coli communis, 6 times (50%).

B. proteus vulgaris, 3 times (25%).

Non-liquefying (or slowly-liquefying), urea-decomposing white staphylococcus, 2 times (16.7%).

No growth, 1 time (8.3%).

(*a*) *B. coli communis* was found in 6 cases (84, 85, 87, 90, 91, 93); in 2 of these (84, 85) the pyelitis was not associated with a cystitis, in 2 (87, 91) a cystitis preceded the pyelitis, and by the time the patient came under our observation the cystitis symptoms and the vesical lesions were slight, in 1 (93) the cystitis preceded the pyelitis, but the symptoms of cystitis and vesical lesions were of the most marked character, while in 1 (90) the pyelitis probably

preceded the cystitis, although the symptoms of either had always been very slight.

In all the cases the urine was acid both from the affected kidney and from the normal kidney, while in one case (85) a small stone was present in the kidney of the affected side; the stone was made up of uric acid and urates. In these, as in fact in all our cases of pyelitis and pyelonephritis, the microorganisms were always present in pure culture.

(*b*) *B. proteus vulgaris* was found in 3 cases (83, 86, 92), in 2 of which the pyelitis was alone, and in 1 (92) the pyelitis was consecutive to a cystitis, although at the time of observation the symptoms of cystitis and the pathological changes in the bladder were very slight.

In all 3 cases the urine from the affected side was markedly alkaline, from the normal side acid and from the bladder either acid, neutral or alkaline. In all 3 cases a renal stone was present, the chemical composition of which was a mixture of calcium and magnesium phosphate and carbonate.

(*c*) *The non- or slowly-liquefying, urea-decomposing white staphylococcus* was found in 2 cases (88 and 89); in both cases the pyelitis was present for a long period of time before any symptoms of cystitis developed, and the latter symptoms were always very slight.

In one case (88) the other kidney had been infected also and had been removed for pyonephrosis and stone, and in this case the urine was usually alkaline both from the bladder and the kidney; while in the other case (89) the other kidney was normal and its urine acid, the urine from the affected kidney alkaline and the urine from the bladder alkaline, neutral or acid on different occasions. In both cases the pyelitis was associated with stone, the chemical composition of which was a mixture of calcium and magnesium phosphate and carbonate as in the case of the infections with the B. proteus.

(*d*) *No growth* was obtained in one case of renal pyuria, nor were tubercle bacilli found after a most careful search. The case was of especial interest, as the infection had undoubtedly died out; 30 years previously the patient had a severe attack of acute cystitis, during which the urine was ammoniacal, the attack following immediately upon a severe instrumental labor. Shortly afterwards

she developed all the symptoms of acute pyelitis, and ever since then there has been constant dull pain in the region of the left kidney, with the passage occasionally of large quantities of pus in the urine. For the past 20 years the urine has been almost constantly acid in reaction. At the operation a large pus kidney was opened and from it a stone of calcium and magnesium phosphate and carbonate taken. The case seems undoubtedly one of infection with one of the microorganisms that decompose urea, the infection subsequently dying out spontaneously.

For many years the symptoms of cystitis have been practically absent.

2. *Mode of infection.*

Of these 12 cases of chronic pyelitis and pyelonephritis, in 5 certainly (83, 84, 86, 88, 89), and probably in one other (90), the infection was carried directly to the kidney by means of the blood or lymph currents from some other focus where the microorganisms were to be found, while in 5 (87, 91, 92, 93, 94) the bladder was the primary seat of infection (cystitis) and the kidney was invaded secondarily, probably by an ascending ureteral infection from the bladder.

It is interesting to again call attention to the fact that in all the cases in which the bladder was infected after the kidney (88, 89, 90), the bladder symptoms and lesions were very slight, while in 4 of the 5 cases in which the bladder was infected before the kidney (87, 91, 92, 94), the cystitis symptoms and presumably the vesical lesions became much less after the pyelitis had been established a certain time, so that at the time when the patient came under our observation cystoscopic examination revealed only localized congestion with perhaps very slight ulceration of the mucous membrane contiguous to the affected ureteral orifice and occasionally also of the trigonum. These observations suggest in the first place the great ability of the bladder to withstand infection if its resistance is not lowered by congestion, trauma or other cause; and in the second place the marked recuperative powers of the bladder without any treatment whatsoever in a certain number of cases.

In Case 85 the infection was carried up the ureter to the kidney, from the vagina, there being a uretero-vaginal fistula.

3. *Other etiological factors* are much more difficult to determine in the cases of pyelitis than in those of cystitis. In 5 of the cases

of chronic pyelitis and in both cases of acute pyelitis, cystitis preceded the pyelitis, and the auxiliary etiological factors in the development of the cystitis were the same as those mentioned under "cystitis," the kidney becoming secondarily infected by way of the ureter. In the other cases, however, where the kidney is primarily affected, in some it is impossible to find any other etiological factors; probably a certain number of microorganisms find their way into the general circulation either from some localized area of infection, or perhaps from the intestinal tract, and in the process of being eliminated through the kidney, set up an infectious pyelitis or pyelonephritis in that organ. In cases 83, 86 and 90 the condition developed so insidiously that it was impossible to find any other etiological factor; in Case 89 it followed a difficult instrumental labor and the attack started with a severe attack of pain; in Case 88 the attack also started with a severe attack of pain and in this case the patient was in a very depleted, anemic condition.

According to many authorities, it is possible for the healthy kidney to eliminate a certain number of microorganisms without suffering any serious harm therefrom; it is probable therefore in these cases either that the number or virulence of the microorganisms was greater than usual, or that the kidney itself was in a somewhat pathological condition (not enough to be determined by the urinary examination) or the general resistance of the patient was lowered by anemia, malnutrition, pregnancy, or some other cause.

It is highly probable that the presence of stone plays but a small rôle in this connection, as in the majority of cases where stone and infection are associated together, the microorganism causing the infection is probably one of those capable of decomposing urea and the infection almost certainly precedes the stone-formation.

Why one kidney only should be affected it is impossible to say in many cases; in Case 81, however, that of an acute cystitis followed by pyelitis, that kidney was affected that had been operated upon for descensus a few days before; while in Case 87, also a cystitis followed by a pyelitis, one kidney, the right, was in marked descensus and this was the kidney that became infected; thus it is probable that these conditions lowered somewhat the resistance of the kidney and rendered infection easier.

4. *The relation between calculus-formation and infection.*

It was a fact of great interest that in every case in which the infection of the kidney or its pelvis was due to a microorganism that rendered the urine from that kidney alkaline, *i. e.* that had the power to decompose the urea, a renal calculus was associated with the infection of the kidney, except in one case (82), a case of acute pyelitis of only 2 weeks' duration.

The chemical composition of the stone in all these cases was the same—a mixture of the carbonates and phosphates of calcium and magnesium, and in the 6 cases in which this variety of stone was found, B. proteus vulgaris was found 3 times, the urea-decomposing white staphylococcus twice, while in one case (94), although there were no bacteria present, the condition had evidently been brought about by a member of the urea-decomposing group of bacteria, which had subsequently died out.

In these cases it is highly probable that the infection precedes the stone-formation; that the alkalinity of the urine from the kidney produced by the microorganism renders possible the deposition of carbonates and phosphates of calcium and magnesium, and that these, subsequently becoming welded together, probably by some of the organic constituents of the diseased urine, form (with the agglutinated bacteria) the nucleus for the calculus which subsequently increases in size by the constant deposition of these salts.

This is born out by the fact that in Case 92, a proteus infection of the renal pelvis, cultures made under the strictest precautions from the centre of the calculus removed by operation showed a pure culture of the proteus bacillus, suggesting not only that the infection preceded the formation of the stone, but also that an agglutinated mass of microorganisms probably formed the nucleus about which the calcium and magnesium salts were deposited.

In only one case of pyelitis caused by a microorganism which did *not* render the urine alkaline (B. coli communis), was a stone found (Case 85); this was a case of uretero-vaginal fistula, produced at the time of labor, and in this case the chemical composition of the stone was uric acid and urates, the former being largely in excess.

In the diagnosis of renal calculus, which is sometimes extremely difficult, as its symptoms may be simulated almost exactly by a pyelitis without stone, by a floating kidney and by other condi-

tions, we have attempted the injection of 5 to 20 ccm. of 1/5 to 1/2 per cent solution of hydrochloric acid through the ureteral catheter into the renal pelvis, retaining it there for from 5 to 15 minutes and then examining the fluid for calcium and magnesium phosphate and carbonate. If only a trace is present, the diagnosis is doubtful, as contamination by the urine might easily cause that; but if present in *comparatively* large amount, the diagnosis of alkaline calculus can be definitely made, as was done in Case 85. The alkaline calculi (calcium and magnesium phosphates and carbonates) seem then to depend upon an alkaline infection, while the acid calculi (uric acid and urates), if associated with pyelitis, which, however, does not seem to be usually the case, are found in cases of acid infection.

X. *Tuberculous Pyelitis and Pyelonephritis.*

Six cases of tuberculous pyelitis and pyelonephritis have been met with, in 2 of which (95, 96) the renal infection occurred alone, in the other 4 (97, 98, 99, 100) cystitis being associated with the pyelitis and pyelonephritis; 1 of the cases (95) was an acute infection, the other 5 were chronic.

In all 6 cases *Tubercle bacilli* were found in the urine (both the urine obtained from the bladder and from the affected kidney), while in all the cases the urine from the other kidney was absolutely normal, *i. e.* in all 6 cases the infection was unilateral.

In all the cases cultures made upon the ordinary media were sterile, *i. e.* we were dealing with cases of pure tuberculous infection.

The urine was always acid, usually quite markedly so; it contained considerable albumin, many pus-cells and usually more red blood-cells than seen in the other forms of pyelitis, as well as renal and ureteral epithelial cells. In some cases the symptoms were rather slight, while in other cases the symptoms, both local and constitutional, were very severe.

The case of acute pyelonephritis due to the tubercle bacillus was of great interest because the clinical picture presented was that of a typical acute nephritis (œdema, nausea and vomiting, the passage of small amounts of dark-colored, smoky urine, etc.); the urine showed casts of all kinds, red blood and epithelial cells and much

albumin, but one was struck by the somewhat greater number of pus-cells than are usually seen in acute nephritis. The urine on careful examination showed Tubercle bacilli, and catheterization of both kidneys showed that the whole condition was referable entirely to one kidney (Tubercle bacilli, casts, pus and blood-cells from that side), while the other kidney was absolutely normal and secreted normal urine. The bladder also was perfectly normal.

The urine of this patient had been examined only 2 months previously and was then normal; no tuberculous lesion was to be found elsewhere.

In Case 95 the infection was undoubtedly carried to the kidney by means of the circulation from a tuberculous focus elsewhere (apex of lung), but in the remaining 4 cases the *mode of entrance* of the microorganisms into the kidney was probably by an ascending ureteral infection, the bladder apparently being infected first; in all these cases marked thickening of the affected ureter could be made out, as also, in all cases except one, much tuberculous ulceration of the vesical mucous membrane adjacent to that ureter.

None of the 6 cases gave a definite tuberculous family history, and in only one (96) was a tuberculous lesion to be found outside of the urinary tract, although probably many, if not all, had a tuberculous gland hidden somewhere about the body.

It was impossible to determine any other especial etiological factors in the development of this condition except anemia, malnutrition and such general factors in certain of the cases.

Cases 96 and 100 were in women under 30 years of age; the other cases were in women between 35 and 50 years of age, and all except one (98) of these latter were married.

XI. *General Consideration of the Results Obtained.*

1. *Bacteriological results and urinary findings.*

Of the 63 cases of *cystitis* studied, careful bacteriological examinations were made in 60, and in these 60 the following microorganisms were found: B. coli communis, 31 times; Staphylococcus pyogenes albus, 7 times; Tubercle bacillus, 6 times; Staphylococcus pyogenes aureus, 5 times; slowly-liquefying, urea-decomposing white staphylococcus, 4 times; B. proteus vulgaris, 2 times; B. typhosus, B. pyocyaneus, unidentified bacillus resembling in many

ways the colon bacillus, each 1 time; while in 2 cases no bacteria were present.

The urine was always acid in 45 cases (B. coli communis, B. tuberculosis, B. typhosus, B. pyocyaneus, unidentified bacillus, 3 cases in which bacteriological examinations were not made), generally acid, although occasionally neutral, and on very rare occasions slightly alkaline in 12 (Staphylococcus pyogenes albus and aureus), alkaline or ammoniacal in 6 (white, urea-decomposing staphylococcus and B. proteus vulgaris). Pure cultures of the microorganism in question were obtained in 59 of the 60 cases studied.

These results show in the first place that the B. coli communis is by far the commonest microorganism found in cases of cystitis, both acute and chronic; while the results of the bacteriological examination of the acute cases demonstrated beyond any doubt that the colon bacillus and the colon bacillus alone can be the cause, and is the cause in the majority of cases, of acute cystitis in women; and in the second place that in the great majority of cases of cystitis the urine is acid, *i. e.* the infection is brought about by microorganisms which under the existing conditions do not decompose urea and thus render the urine alkaline or ammoniacal.

The ordinary staphylococci seem to have this urea-decomposing property in a slight degree, and thus in the cases where they are the infecting microorganisms, the urine may be acid (although less so than normally), neutral or very occasionally slightly alkaline.

Albuminuria, if present at all, was slight in all these cases except those in which the cystitis was associated with pyelitis.

In 9 of these cases, pyelitis or pyelonephritis was associated with the cystitis; in 4 cases the former was the primary infection, in 5 cases the latter.

Of *pyelitis* and *pyelonephritis*, 20 cases were studied bacteriologically, and in these were found B. coli communis, 7 times; Tubercle bacillus, 6 times; B. proteus vulgaris, 4 times; urea-decomposing white staphylococcus, 2 times; while in one case no bacteria were found; in all cases pure cultures of the microorganism were obtained.

The urine from the affected kidney was acid 14 times (B. coli communis, Tubercle bacillus, cases where no bacteria were present) and alkaline in 6 (B. proteus vulgaris, urea-decomposing white staphylococcus); in no case was the urine obtained from the kidney

ammoniacal, the ammoniacal changes apparently taking place in the bladder, if that organ is also infected. Albumin was present in the urine in all these cases, usually in considerable amount, and the relation between the albuminuria and the pyuria is the most valuable method we have of differentiating pyelitis from cystitis in those cases where cystoscopic examination and ureteral catheterization cannot be carried out.

Thus in the 80 cases of infection of the urinary tract studied bacteriologically, the B. coli communis was found 38 times; the Tubercle bacillus, 12 times; the Staphylococcus pyogenes albus, 7 times; the Staphylococcus pyogenes aureus, 5 times; the B. proteus vulgaris, 6 times; the white, urea-decomposing staphylococcus, 6 times; the B. typhosus, B. pyocyaneus and an unidentified, colon-like bacillus, each once; while in 3 cases no bacteria were present.

2. *Mode of entrance of the infection and other etiological factors.*

A consideration as to the mode of entrance of the infection tells us that in the great majority of cases of cystitis, except probably the tuberculous, the infection is introduced through the urethra, usually by catheter, while a descending infection from the kidney and infection from the intestinal tract by direct transmission or by means of the blood and lymph currents must be considered as possible modes of infection, as also a direct extension from some abscess cavity localized in the pelvis, or from some other focus of infection.

In the case of pyelitis, ascending infection from the bladder and infection carried by the blood or lymph currents from some other portion of the body were found with about equal frequency. In tuberculous cases the common mode of infection is probably one from a tuberculous focus in some other portion of the body carried by the blood or lymph currents.

One is at once struck, on looking over the cases in our series, by the fact that in a great number microorganisms are found which usually possess but slight pyogenic properties; as, for example, the B. coli communis and the Staphylococcus pyogenes albus.

It seemed therefore probable, although the microorganisms themselves were the direct cause of the condition (cystitis), that other etiological factors played an important rôle in its development, and a consideration of our cases fully justifies this probability.

The accessory etiological factors in the causation of cystitis were

those that in any way reduced the resisting power of the bladder, such as anemia, malnutrition, trauma (usually due to catheterization, foreign body or operation), congestion of the bladder produced by pressure of other organs or tumors or by adhesions, retention of urine, the trauma and congestion of pregnancy and labor, neoplasm, etc.

In pyelitis these accessory etiological factors were more difficult to determine, but in some cases local trauma of the kidney and in others a general lowering of resistance due to anemia and malnutrition were definitely shown; in others the condition was consecutive to pregnancy and labor. That these accessory etiological factors are of the greatest importance one is compelled to admit, not only from a consideration of the cases themselves but from the experimental work of Rovsing, Melchior and others, by whom it was shown that cultures of various bacteria could be injected into the bladders of healthy animals without any infection being produced unless the resistance of that organ was lowered by trauma, congestion, retention of the urine, etc.

In the case of the Tubercle bacillus and of those bacteria that possess in a marked degree the power to decompose the urea, rendering the urine alkaline or ammoniacal, the presence of these accessory factors does not seem so necessary to the production of the infection.

XII. *Bacteriological Results Obtained by other Observers.*

No attempt will be made here to more than briefly state the bacteriological findings of some of the well-known workers in this field.

In passing, we will mention that cases of cystitis have been described, due to, or at least associated with, the Filaria sanguinis hominis, the Bilharzia, the Echinococcus, yeast and the Amœba coli; as well as after various chemicals hitherto spoken of; all these conditions, however, are extremely rare and will not be considered in our summary.

In describing their bacteriological findings, many observers have given new names to bacteria which subsequent investigations have shown to be identical with microorganisms already known.

Thus the B. proteus vulgaris of Hauser has been described by

various observers as the Bacterium vulgare and the Urobacillus liquefaciens septicus.

Krogius, Achard and Renault identified Albarran and Hallé's "bactérie pyogène," and Clado's "bactérie septique del a vessie" with the B. coli communis, while Krogius' "bacille non-liquefiant," and what Morelle and Denys regarded as B. lactis aërogenes (Escherich), have been subsequently shown to be in all probability identical with the same bacillus.

Schmidt and Aschoff believe that many of the new species described by Rovsing are in reality but varieties of the B. coli communis, which Melchior thinks especially probable in the case of Rovsing's "Cocco-bacillus ureæ pyogenes."

When we consider the marked pleomorphism of the colon bacillus, it is not to be wondered at that these variations from the common type have been met with, and have caused some observers to regard their microorganisms as new species.

The exact status of members of the micrococcus and staphylococcus groups is also in a rather unsatisfactory state, and in this case also undoubtedly many of the new species described are but varieties of well-known species that have acquired certain atypical characteristics, probably by their longer or shorter habitat in a comparatively unfavorable medium.

Lundström, in 1890, from alkaline cystitides, isolated Staphylococcus ureæ candidus and Staphylococcus ureæ liquefaciens, and from acid cystitides Streptococcus pyogenes.

Schnitzler, in 1892, found the B. proteus vulgaris in 16 of 25 cases of cystitis, in 9 of these in pure culture; the great frequency of this microorganism in these cases is probably due to the fact that Schnitzler's cases were mostly those of women with gangrenous uterine carcinomata in the discharge from which this microorganism is so frequently found; Schnitzler found that cultures of this microbe injected into the bladder of healthy rabbits would give rise to cystitis without there being any trauma to the bladder or congestion of its mucous membrane.

Krogius found the B. coli communis in 16 of 22 cases of cystitis, in 14 of these in pure culture; 6 of these were associated with an ascending pyelonephritis; all the colon cases had acid urine.

Rovsing reports a long series of cases of infection of the urinary tract, divided as follows: 22 cases of bacteriuria, all due to the

B. coli communis, of which 10 were cases of pure bacteriuria and 12 cases where the urine contained a few pus-cells (see our cases 17 and 20); 21 cases of pyelitis without cystitis, in 19 of which the B. coli communis was present in pure culture, in 2 associated with micrococci (a staphylococcus once, a streptococcus once); 11 cases of pyelitis complicated by cystitis, with ammoniacal urine, in which the Staphylococcus aureus was found 3 times in pure culture, the Staphylococcus albus twice in pure culture, once associated with the Streptococcus pyogenes, once with the B. proteus vulgaris, while the B. liquefaciens, B. longus liquefaciens and Sarcina flava were each found once in pure culture, and the B. coli communis once in association with the Streptococcus ureæ; 3 cases of pyelitis complicated by cystitis, with acid urine, in 2 of which the tubercle bacillus, in 1 the B. typhosus, were found, each in pure culture; 6 cases of Rovsing's "catarrhal cystitis," all due to various micrococci (it would seem that these cases should really be placed under the head of "bacteriuria"); 13 cases of suppurative ammoniacal cystitis, where the B. coli communis was associated with ammoniogenous microbes; 37 cases of suppurative ammoniacal cystitis, without the B. coli, where various bacilli and cocci were found, as Staphylococcus albus, Coccobacillus ureæ liquefaciens, B. proteus vulgaris, B. longus ureæ, Staphylococcus pyogenes aureus, Streptococcus pyogenes ureæ, Tetracoccus flavus sarciniformis, etc.; 13 cases of suppurative acid cystitis, in 3 of which the tubercle bacillus was found, in 3 the gonococcus, in 1 the gonococcus and the B. coli communis, in 3 micrococci (Streptococcus pyogenes 2, Diplococcus aureus 1), and in 3 a non-motile colon bacillus. Thus it will be seen that the striking characteristics of Rovsing's cases are first the large number of new species that he describes and second the predominance of cases with ammoniacal urine.

He especially opposes the view that the colon bacillus is the cause of cystitis in many cases, thinking that where it does occur, its presence is more or less accidental, the infection having been caused by some other microorganism, which is either associated with the colon bacillus or has been driven out by it.

Ample proof of the erroneousness of this view is furnished by the findings in our cases of acute cystitis.

Probably one reason why Rovsing's results differ so materially from those of the majority of other observers is because of the large

proportion of cystitides in old men with enlarged prostate, vesical calculus, marked dilatation of the bladder and urinary retention found among his cases.

In Melchior's 35 cases of cystitis, in 26 the urine was acid, in 9 alkaline or ammoniacal; the bacteria found were as follows: B. coli communis 24 times, 17 times in pure culture; Streptococcus pyogenes 4 times, 3 times in pure culture; Proteus of Hauser (B. proteus vulgaris) 4 times, once in pure culture; Tubercle bacillus 3 times, twice in pure culture; Diplococcus ureæ liquefaciens (new variety) 3 times, twice in pure culture; Staphylococcus ureæ liquefaciens 3 times, once in pure culture; Streptobacillus anthracoides (new variety) 3 times, never in pure culture; Gonococcus and B. typhosus each once in pure culture. Melchior also reports 5 cases of pyelonephritis, 2 due to the B. coli communis, 2 to the Streptococcus pyogenes and 1 to the B. typhosus.

Schmidt and Aschoff up to the time of the publication of their monograph (1893) had collected 60 cases of cystitis in which the B. coli communis was found in pure culture, and 13 cases in which the B. proteus vulgaris was found in pure culture; all the former had acid, all the latter alkaline or ammoniacal, urine.

Rostoski collected 120 cases of cystitis from the literature, including 6 of his own, in which the B. coli communis (or a microorganism closely related to it) was found 80 times, B. proteus vulgaris 11 times, and Tubercle bacillus, B. typhosus, Streptococci and Micrococci (among which Gonococcus was found 3 times) were also found; in most cases the microorganism was in pure culture and the urine was always acid in those cases in which the colon bacillus occurred alone.

Albarran, Hallé and Legrain, in 1898, collected 304 cases of cystitis from the literature, in 131 of which was found the B. coli communis, 89 times in pure culture; other microorganisms found were: B. proteus vulgaris, Streptococcus pyogenes (18 times), Gonococcus, Tubercle bacillus; these were the microorganisms frequently found; the rare microbes were B. typhosus, Diplococcus of Fränkel, Diplococcus of Friedländer; the exceptional microbes, B. longus ureæ, B. crassus, Streptobacillus of Melchior, Urobacillus of Maddox, Micrococcus subflavus, Coccobacillus of Rovsing, Sarcina alba, etc.

Other microorganisms which have been found in cystitis in ex-

ceptional cases are the Pseudo-diphtheria bacillus, the Influenza bacillus, although the sole case in which it has been described is very doubtful, and the B. pyocyaneus; although seen several times before in cystitis in connection with other microorganisms, the case of cystitis due to this last bacillus (Case 13 of our series) is, so far as I know, the only one in which the direct etiological connection between cystitis and this microorganism has been definitely proven.

In these cases, both males and females have been included. It will perhaps be of interest to study separately the bacteriological flora in the infections of the urinary tract in either sex in the 2 most important series of cases, those of Rovsing and Melchior.

The former's results are as follows: In *women*, *pyelitis without cystitis*, 16 cases, B. coli communis 14 times in pure culture, once associated with a staphylococcus, once with a streptococcus (could not be cultivated); *pyelitis with cystitis*, 3 cases, 2 with ammoniacal urine (1 due to the B. coli and Streptococcus ureæ, 1 to Staphylococcus aureus), 1 with acid urine (due to Tubercle bacillus); *suppurative ammoniacal cystitis*, 9 cases, 2 cases due to the B. coli and a coccus, to the B. coli and a Staphylococcus, and to the Staphylococcus pyogenes albus alone respectively, and 1 case due to the B. coli and diplococcus, Coccobacillus ureæ pyogenes, and B. longus ureæ respectively; *suppurative acid cystitis*, 6 cases, 1 due to the Tubercle bacillus alone, 2 to that microorganism in association with the B. coli communis, and 3 to the B. coli communis (although Rovsing regarded some of the characteristics of these last as atypical).

In *men* the picture presented was decidedly different, and was as follows: *Pyelitis without cystitis*, 5 cases all due to the B. coli communis; *pyelitis with cystitis, with ammoniacal urine*, 9 cases, 2 due to the Staphylococcus albus and aureus respectively, and 1 to the B. liquefaciens, B. longus liquefaciens, Sarcina flava, Staphylococcus albus in association with Streptococcus pyogenes, and Staphylococcus in association with B. proteus vulgaris respectively; *catarrhal ammoniacal cystitis*, 6 cases, due to various urea-decomposing, non-pyogenic staphylococci and diplococci; *suppurative ammoniacal cystitis*, 41 cases, in which a great variety of microorganisms were found, as follows, Staphylococcus albus 10 times, Staphylococcus aureus 9 times, B. proteus, B. longus ureæ, Streptococcus ureæ pyogenes and a urea-decomposing diplococcus 3

times each, Tetracoccus flavus sarciniformis, B. coli in association with a staphylococcus and B. coli in association with a coccus twice each, and B. coli in association with B. proteus, B. coli in association with B. longus ureæ, B. coli in association with a streptococcus, and B. coli in association with B. crassus once each; *suppurative acid cystitis*, 7 cases, 4 due to the Gonococcus, 2 to the Streptococcus pyogenes, 1 to the Diplococcus aureus.

It will thus be seen that in Rovsing's series the male cases are in preponderance, except in the case of pyelitis without cystitis, where there were 16 cases in women to 5 in men; while in pyelitis with cystitis the female cases were only 3 to the men's 10; in catarrhal ammoniacal cystitis 0 to 6; in suppurative ammoniacal cystitis 9 to 41, and in suppurative acid cystitis 6 to 7.

In Melchior's series of cases of *cystitis* the results were as follows: In *women*, B. coli communis 10 times in pure culture, once in association with the Tubercle bacillus, and twice in association with B. proteus; B. proteus, B. typhosus and Diplococcus uræa liquefaciens once each in pure culture; in *men*, B. coli in pure culture 9 times, B. coli in association with Streptococcus once, and once in association with Staphylococcus ureæ liquefaciens and Streptobacillus anthracoides, Streptococcus and Diplococcus ureæ liquefaciens twice each, once in pure culture and once in association with other microorganisms, B. proteus in association with Staphylococcus pyogenes once, and Gonococcus, Tubercle bacillus and Staphylococcus ureæ liquefaciens once each in pure culture.

Melchior gives but 5 cases of pure pyelonephritis, 3 in the female (due to B. coli communis, B. typhosus and Streptococcus pyogenes respectively), 2 in the male (due to B. coli communis and Streptococcus pyogenes respectively).

It will thus be seen from a consideration of these cases that the B. coli communis is probably found in a greater proportion of cases of cystitis in the female than in the male, probably due in part to the close proximity of the vulva to the anus and in part to the shortness of the female urethra.

XIII. *Polymorphism of Various of the Bacteria (1), and Agglutination of the Bacteria by the Patients' Serum in Cystitis and Pyelitis (2).*

1. *Polymorphism of various of the bacteria.*

One is struck in a bacteriological study of this kind at the distinct polymorphism that certain of the bacteria present. These changes from what may be considered the normal are probably to be ascribed to a longer or shorter growth upon media and under conditions more or less favorable than ordinary. That this is so in the cases of many bacteria one has but to mention the marked changes in the morphology of the Tubercle bacillus according to the mode of preparations of its culture, the decrease of virulence of the Streptococcus pyogenes and various Staphylococci after long growth on unfavorable media and their marked increase in virulence if subjected to extraordinarily favorable circumstances, the variations in motility and virulence of the B. typhosus under varying circumstances, etc., etc.

In fact it seems highly probable that bacteria show in many ways whether the media upon which they grow and the circumstances surrounding their growth are favorable or unfavorable.

In the case of the infections of the urinary tract, we have a series of conditions especially favorable to developing polymorphism in the microorganism found. Thus we have the varying degrees of resistance of the patient to infection, depending on many factors (anemia, malnutrition, etc.); the condition of the urinary tract, whether it has recently undergone trauma, is congested or locally anemic, etc.; the number of microorganisms originally introduced, and their virulence, an especially important point when we consider the marked variations in the virulence of cultures of the colon bacillus found in the intestinal tract in health and in disease, and of the staphylococci and streptococci, depending on whether they have been living a parasitic or a saprophytic existence for some time; the condition of the urine, whether it contains no albumin, a trace, a small or a considerable amount; the length of time the infection has been present, and whether the microorganisms are in pure culture or not. All these factors undoubtedly are of importance in exactly determining the especial characteristics of the microorganism in any especial case.

(*a*) *B. coli communis.*—Marked changes were seen in the different cases in the characteristics of this microorganism, the commonest of the microbes found in cystitis, pyelitis and pyelonephritis, the microorganism presumably in the great majority of cases coming from contamination with the fæcal discharges of the patient. Thus in some cases this bacillus would give rise to an infection only a degree above a pure bacteriuria, while in other cases the pathogenic and pyogenic properties of this microbe were quite as marked as seen in the case of the most virulent of microorganisms. As to the morphology of the bacillus, in some cases it was a typical, rod-shaped bacillus, in other cases it approached in its shape very closely to a coccus, a diploid arrangement was frequently met with, and the length and breadth of this microorganism differed in the different cases, in some very markedly.

The *motility* also differed markedly; in one case (as severe a cystitis as we have ever met with, Case 40) the microorganism was almost as actively motile as the B. typhosus, in other cases almost non-motile, the usual condition being one of rather sluggish motility. The *growth* on the various media also varied markedly, in some cases the growth was profuse and rapid, in other cases scant and slow; marked differences were seen in the length of time required to produce indol and acidify and coagulate milk, and in the quantity of gas produced in glucose-agar; in gelatine the growth was sometimes more opaque, sometimes more transparent; in none of our cases, however, was the gelatine liquefied. I was unable to demonstrate that this microorganism had the ability to split up the urea in the urine to the slightest extent, although I kept sterile urine to which the colon bacillus had been added for a week in the thermostat; perhaps, however, this was too short a time, as Hallé and Dissard state that they got evidences of this decomposition with the colon bacillus in from 3 to 30 days; Rostoski, however, found the urine still acid in his cases after it had been kept for from 30 to 45 days in the thermostat. In some cases the B. coli seems undoubtedly to increase the normal acidity of the urine; in no case did I meet with any evidence that it decreased it.

As to the relation between morphological and cultural peculiarities and virulence, in certain of the cases it undoubtedly seemed as if the less coccus-like the microorganism, the more marked the motility and the more rapid the growth and the changes in the

various media; the more marked was its virulence. It will be easily seen, from a consideration of the variations which are met with in this microorganism, why what was undoubtedly a variety of this microorganism has been regarded as a new species and described under a new name in a number of cases by various observers.

(*b*) *Staphylococci.*—The whole question of the relation between the various members of the staphylococcus group and their differences is in such an unsettled condition that I will here give simply the objective results of my observations in this connection without attempting to draw any conclusions therefrom.

The staphylococci met with in our series of cases were the Staphylococcus pyogenes albus and aureus, and a white staphylococcus, noted especially for its rapid and powerful action in decomposing urea and in the slowness with which it liquefied gelatine.

There were some slight differences seen in the size of the micrococci in different cases; there was not sufficient evidence present in any of the cases to define the microorganism as a diplococcus, although the diplococcus arrangement was frequently met with in a certain number of the microbes.

There was also noted some variation in the rapidity of growth and in the production of the changes in the various media; in the case of an especially severe case of cystitis due to the Staphylococcus aureus (Case 35), the growth was very luxuriant and the changes produced in the various media very rapid. A white staphylococcus was met with in a number of cases, always in association with an alkaline or ammoniacal urine, the chief peculiarities of which were its power to produce rapid decomposition of urea and its slowness in liquefying gelatine. Its growth on agar was profuse and rather more waxy than that of the ordinary Staphylococcus pyogenes albus, it gave a white opaque growth on potato, which later became more opaque and very dry, while in gelatine a rather profuse white growth was seen along the line of stab and a white moist growth on the surface. Its liquefying power was very slight, and in the earlier cases in which this microorganism was met with, after no signs of liquefaction were noted after from 7 to 10 days, it was supposed that the microorganism was not a liquefier of gelatine, but later observations seem to show that it has a slight liquefying power, which begins to bring about liquefaction in from 2 to 4 weeks.

Whether this microorganism was originally one of the ordinary staphylococci, which has acquired these peculiarities of growth on account of its habitat or not, it is impossible to say.

Its most striking peculiarity is the rapidity with which it decomposes urea, thus rendering the urine alkaline or ammoniacal.

In the case of the ordinary Staphylococcus pyogenes albus and aureus the urine was usually acid, sometimes neutral and very occasionally alkaline.

As to the *chromogenic properties* of the staphylococci, several interesting observations were made: In Case 29 and in Case 25 the growth from the urine upon the agar-plate consisted of light-yellow colonies; transplantations from this on potato gave colonies of a deeper yellow color, while a transplantation from this upon agar, and from the latter upon agar again, gave colonies with the typical orange color of the Staphylococcus pyogenes aureus.

Also in one other case the same was noted as regards the changes in color, except that in this case the original colonies were almost white, although again by successive transplantations they finally became of the typical orange.

These and allied observations seem to show that there is a close relationship between some, at least, of the various members of the staphylococcus group, and to suggest that possibly these related members all sprang from the same microorganism, the changes in their characteristics depending upon their history since that time, whether their existence had been parasitic or saprophytic, whether the media upon which they had lived had been favorable or unfavorable, etc.

2. *Agglutination of the bacteria found in cystitis and pyelitis by the serum of the patient.*

On account of lack of time but few observations have been made concerning this interesting question—the agglutination by the patient's serum of the microorganism found in the cases of cystitis or pyelitis. Obviously this can only be studied satisfactorily in the case of motile bacteria, *i. e.* bacilli. This has been tried in but 3 of our cases, cases 26, 40 and 92.

Case 40 was a cystitis of many years' duration in a girl who had always been delicate; the B. coli communis was found in pure culture and the microorganism was the most actively motile and the most rapid grower of all our specimens of the colon bacillus; the

agglutination test was made by the method usually in vogue in the case of the typhoid bacillus, the blood being collected in a pipette with an end of fine calibre and the serum after it had separated from the clot, being tested with an 18-hour culture of the bacillus in bouillon; in dilution of 1: 10 clumping was distinct in 10 minutes and almost complete in 30 minutes, with corresponding loss of motility; in dilution of 1: 20, the reaction was almost as positive at the end of 30 minutes, while in dilution of 1: 50 motility was impaired and clumping beginning in 10 minutes, the reaction was positive in 30 minutes, and clumping was almost complete and motility almost entirely diminished in 60 minutes.

Case 26 was one of acute cystitis, followed by acute ascending pyelonephritis, due to a very virulent B. proteus vulgaris in pure culture; in dilution of 1: 10 the reaction was marked in 10 minutes and practically complete in 30 minutes, while in dilution of 1: 50 the reaction was distinctly beginning in 10 minutes, positive in 30 minutes and almost complete in 60 minutes.

Case 92 was one of a chronic pyelitis of 2 years' duration, consecutive to a cystitis of 4 years' duration, the latter condition having almost entirely cleared up spontaneously. The microorganism found was the B. proteus vulgaris in pure culture; in dilutions of 1: 10 the reaction was suspicious after 30 minutes and suggestive after 60 minutes, there being some clumping and impairment of motility; in dilutions of 1: 50 the reaction was not obtained in 60 minutes.

In Case 14, an acute cystitis, due to the B. typhosus, unfortunately the microorganism was not tested with the serum of the patient; it was, however, tested with the serum of a patient with a typical case of typhoid fever, and gave the most positive reaction in a dilution of 1: 80.

These results, although few in number, are of interest, and suggest in the first place a method of testing for the microorganism in doubtful cases, and in the second place a means of differentiating slightly different members of the same group of bacteria, besides suggesting the development of possible reactive tendencies against the infection in the organism as a whole in this class of cases.

XIV. *Therapeutic Suggestions derived from the Bacteriological Findings.*

It would be obviously out of place here to do more than speak of a few therapeutic measures which are directly suggested by the bacteriological findings.

In the first place, the urine will probably be a poorer medium for the growth of bacteria, the lower the specific gravity and, consequently, the less the amount of albumin and urea present; for that reason water should be given in large amounts, preferably by mouth, but if this is not feasible by rectal enemata or by subcutaneous injection; this is of especial importance in acute infections and in all forms of pyelitis. Besides lessening the ability of the microorganisms to rapidly reproduce themselves, this is of advantage in thoroughly flushing out the kidneys and bladder, and getting rid, as far as possible, of collections of purulent matter.

In the second place, it is obviously of advantage to administer substances which, in a certain degree, render the urine antiseptic, although of course this must affect the microorganisms lying in the deeper tissues of the kidney and bladder to a much less extent than those on the surface of the pelvic (of kidney) or vesical mucous membrane; such substances are urotropin, cystogen, salol, etc., and in our hands have proven of great value in the acute infections, although of much less value in those cases where the condition has become chronic.

In the third place, in those cases associated with an alkaline condition of urine it would seem proper to administer substances by the mouth tending to render the urine acid, as boracic, benzoic and camphoric acids, while in those cases where the urine is acid, alkalies should be given to render the urine alkaline (as bicarbonate of soda or citrate of potash), the reason for these procedures being that it would seem probable that the urea-decomposing microorganisms have their growth hindered by the presence of an excess of acid, while on the other hand the microorganisms which retain the acidity of the urine or render it more acid would seem to have their growth distinctly inhibited by an alkaline condition of urine. The same condition of inhibition of growth would probably be produced in any case by a *great excess* of either acid or alkali in the urine, the bactericidal properties of the former of which have recently been shown by Rostoski.

In the fourth place in urinary hyperacidity without infection but with symptoms suggestive of cystitis, the hyperacidity should be corrected by the administration of alkalies and the neurasthenical manifestations treated in the proper way.

And in the fifth place it is essential that the resisting power of the patient be increased by a careful attention to the general condition of her health, the correction of any disorders of nutrition or digestion, or of any diminution in the constituents of the blood, if such conditions are present; and the careful regulation of the personal hygiene.

Of course in many cases other measures besides the ones just mentioned have to be employed, such as topical treatment, irrigations, instillations (nitrate of silver has proven of most value to us in these connections), operative treatment of various kinds, etc., and the above are but the suggestions regarding the general medical treatment of cases of cystitis, pyelitis and pyelonephritis derived directly from the bacteriological study of the cases.

A consideration of the results obtained in our investigations will, we think, justify the following conclusions:

Conclusions.

1. The direct cause of the infection of the urinary tract in women is the invasion and multiplication of some form of microorganism.

2. The commonest cause of these infections is the B. coli communis, which a consideration of the cases of acute cystitis definitely proves can and does in a large number of cases set up a true infection without the aid of any other microorganism.

3. Marked variations are seen in the virulence of this microorganism and in its pyogenic properties.

4. Other microorganisms frequently found are the Tubercle bacillus, various staphylococci and the B. proteus vulgaris; while numerous varieties of microorganisms have been less frequently and occasionally met with, as the B. pyocyaneus and Typhoid bacillus.

5. The proportion of cases of infection due to the B. coli communis is greater in women than in men, probably due to the close proximity of the female urethra to the anus.

6. Besides the entrance of the microorganisms, other factors are

in most cases essential to the development of a cystitis; the chief of these factors are anemia, malnutrition, trauma of and pressure upon the bladder, congestion of the bladder and retention of urine.

7. In cystitis the chief mode of infection is by the urethra, although one must also consider as possibilities a descending ureteral infection from an infected kidney, pyogenic metastasis by means of the blood and lymph currents, and direct transmission of the microorganisms from the intestinal tract, or from some adjacent focus of infection.

8. In pyelitis and pyelonephritis the usual modes of infection are along the ureter from an infected bladder, and by means of the blood and lymph currents; in our cases these modes of infection were found about equally represented.

9. In the great majority of cases of cystitis, both acute and chronic, and in the majority of cases of pyelitis and pyelonephritis, the urine is acid.

10. In the cases in which the urine is ammoniacal, the infection can be produced without the aid of any of the accessory etiological factors mentioned above, the irritation of the ammoniacal urine apparently being sufficient to render the bladder susceptible to infection.

11. In the case of infections of the kidney due to a urea-decomposing microorganism, a stone is very likely to be present if the case is at all chronic.

12. Certain conditions exist which present most of the symptoms of cystitis but no infection; the most difficult of which to diagnose is probably urinary hyperacidity of neuropathic origin, the successful treatment of which depends upon the successful recognition both of its urinary features and its general basis.

13. Although the diagnosis of renal infections can be made with absolute certainty only by ureteral catheterization, a probable differentiation between renal and vesical infections can be made by a careful study of the urine alone.

14. Tuberculous infections of the urinary tract frequently occur with no other demonstrable tuberculous lesions elsewhere in the body. Probably a tuberculous gland would be demonstrable postmortem in most of these cases.

15. The colon bacillus seems to be the commonest cause of

pyelitis, while the B. proteus vulgaris and members of the staphylococcus group are also found less frequently.

16. And finally to be able to thoroughly understand the cases of cystitis, pyelitis and pyelonephritis brought to our notice, to make the proper diagnosis, to inaugurate and carry out a rational line of treatment and to give a correct prognosis, a careful chemical and bacteriological study of the urine is absolutely essential.

BRIEF DIGEST OF CASES OF CYSTITIS, PYELITIS, AND PYELONEPHRITIS.

Acute Cystitis.

Chronic Cystitis (non-tuberculous).
A. Cystitis alone.
B. Cystitis with Pyelitis.

Tuberculous Cystitis.
A. Cystitis alone.
B. Cystitis with Pyelitis.

Conditions simulating Cystitis but no Infection.
A. Hyperacidity.
B. Other conditions.

Acute Pyelitis.

Chronic Pyelitis.
A. Pyelitis alone.
B. Pyelitis with Cystitis.

Tuberculous Pyelitis.
A. Pyelitis alone.
B. Pyelitis with Cystitis.

DIGEST OF CASES OF CYSTITIS, PYELITIS AND PYELONEPHRITIS.

Cases of Acute Cystitis.

1. F. C. B. *Operation:* salpingo-oöphorectomy and cystectomy, for a large ovarian cyst with many dense adhesions. *Cystitis* developed on 17th day with usual symptoms. *Urine:* large numbers of pus-cells, some red blood and epithelial cells, acid, faint trace of albumin. *Bacteriological examination: B. coli communis. Treatment:* urotropin grs. x, three times a day, soda and lithia. *Result:* cure within less than three weeks' time.

2. C. A very neurotic patient with some frequency of micturition since an attack of pneumonia a short time before. The urine was normal and the bladder examination negative before the operation. *Operation:* appendicectomy, for chronic appendicitis with adhesions to neighboring organs, including the bladder. *Cystitis* developed on the 8th day. *Urine:* enormous numbers of pus-cells, some red blood and epithelial cells, trace of albumin, acid. *Bacteriological examination: B. coli communis. Treatment:* urotropin and soda by mouth. *Result:* cure.

3. E. *Diagnosis:* salpingitis and perioöphoritis. *Operation:* double salpingectomy; left oöphorectomy; suspension of uterus; freeing of adhesions (many about bladder). The patient was in a very asthenic and anemic condition previous to the operation. She was catheterized 7 times in all, on the 3 days following the operation. *Cystitis* developed on the 48th day, *i. e.* 45 days after she had been catheterized. *Urine:* large numbers of pus-cells, some red blood and epithelial cells, faint trace of albumin, acid. *Bacteriological examination: B. coli communis. Treatment:* soda by mouth, Blaud's pills, forced feeding, sunshine. *Result:* cured.

4. E. *Cystitis* developed after birth of 2d child (a short time before), associated with discharge from uterus and (according to patient) escape of gas from uterus, but none from bladder. *Urine:* many pus-cells, some red blood and epithelial cells, acid, faint trace of albumin. *Bacteriological examination: B. coli communis.* Patient was seen but once and did not return.

5. F., age 65 yrs. *Operation:* removal of carcinomatous masses from pelvis; many adhesions. *Cystitis* developed on the 5th day. *Urine:* many pus-cells, some red blood-cells and epithelial cells, acid, trace of albumin. *Bacteriological examination: B. coli communis. Treatment:* urotropin grs. x, three times a day, soda and lithia. *Result:* cured.

6. G. *Complaint:* sterility. *Operation:* dilatation and curettage. No note made of catheterization, but it was probably performed several times. For some time previous to the operation there had been a very profuse, purulent vaginal discharge, containing enormous numbers of staphylococci. *Cystitis* developed shortly after the operation. *Urine:* a number of pus-cells, red blood-cells and epithelial cells, trace of albumin, acid (faintly). *Bacteriological examination: Staphylococcus pyogenes albus* in small number. *Result:* cured.

7. H. S. H. The patient had been in extremely poor health for some time, and was much emaciated and very anemic. Three weeks before being seen she complained of a slight burning pain on micturition, which steadily increased. On examination the *urine* was found to contain very many pus-cells, a considerable number of red blood-cells, epithelial cells; it was acid and contained a bare trace of albumin. *Bacteriological examination* showed *Staphylococcus pyogenes albus.* Another culture made a few days later showed a diminished number of pus-cells and fewer staphylococci. The *cystoscopic examination* showed a general reddening of the bladder, with extreme congestion of the trigonum. The patient was given soda grs. x, 3 times daily by mouth, and a daily irrigation of borax and soda solution for 10 days, combined with general tonic treatment. *Result:* cured. This case is of interest (since the patient had never been catheterized) in showing the important rôle malnutrition and anemia play in the development of cystitis.

8. L., a very pale, anemic woman (hemoglobin = 57%). *Operation:* hysteromyomectomy for a large myomatous uterus. The bladder was freed from the tumor and pulled down, necessitating much handling.

Cystitis developed on the 14th day, being marked in this case by much more pain than is usually seen and associated with a temperature of over 100° F. for several days. *Urine:* acid, faint trace of albumin, many pus-cells, some red blood-cells and epithelial cells. *Bacteriological examination: B. coli communis. Treatment:* soda by mouth, tonic treatment, and large quantities of water. *Result:* cured.

9. M. Pale woman, extremely anemic (hemoglobin = 25%). *Operation:* hysteromyomectomy for large myomatous uterus with many adhesions. The patient had some frequency of micturition before operation, due to the pressure of the tumor, but the urine was absolutely normal. *Cystitis* developed on the 9th day. *Urine* showed many pus-cells and a considerable number of red blood and epithelial cells; it was usually acid in reaction and contained a trace of albumin. *Bacteriological examination: Staphylococcus pyogenes albus. Treatment:* urotropin (grs. x, t. i. d. for 20 days) and soda, combined with Blaud's pills and forced feeding. *Result:* cured. *Urine*, also seen 6 months later, was perfectly normal.

10. M. The patient had for two years suffered with difficulty in micturition, due to an enormous myomatous uterus which pressed upon the bladder; the urine, however, was absolutely normal. *Operation:* hysteromyomectomy. *Cystitis* developed several days after the operation and the *urine* showed many pus-cells, some red blood and epithelial cells, was acid in reaction and contained a trace of albumin. *Bacteriological examination: Staphylococcus pyogenes albus. Treatment:* urotropin (grs. x, t. i. d.) and soda by mouth. *Result:* cured.

11. J. H. M. *Diagnosis:* double hydrosalpinx, myomatous uterus, extensive pelvic inflammatory disease and dense adhesions. Some frequency of micturition before operation due to pressure of tumor and adhesions, but urine was absolutely normal. *Operation:* hysteromyomectomy; double salpingo-oöphorectomy. *Cystitis* developed on the 20th day; the *urine* showed a moderate number of pus, and a few blood and epithelial cells; was acid in reaction and contained a bare trace of albumin. *Bacteriological examination: B. coli communis. Treatment:* urotropin (grs. x, t. i. d. for 16 days), soda and lithia, and Blaud's pills (patient was very anemic). *Result:* cured.

12. F. H. M. Patient had a markedly relaxed vaginal outlet and a retroflexed uterus; both kidneys were in descensus and there was a general enteroptosis. There had been an increased frequency in the desire to urinate since the childbirth, at which the outlet was torn, but the urine was perfectly normal. *Operation:* dilatation and curettage; resection of the relaxed vaginal outlet; suspension of the uterus; suspension of the right kidney. The patient was catheterized an exceptionally great number of times after the operation (between 15 and 20). *Cystitis* developed on the 17th day; the *urine* was acid and contained a few pus-cells, red blood-cells and epithelial cells, and the faintest possible trace of albumin. *Bacteriological examination: B. coli communis. Treatment:* urotropin (grs. x, t. i. d. for 14 days), soda and lithia. *Result:* cured.

13. R. This patient 5 years before had complained of some pain in the trigonal area of the bladder, but the urine, repeatedly examined, was always found to be absolutely normal. The total acidity was not determined, but there is a strong probability that, at that time, the case was one of hyperacidity, as the patient was extremely nervous and complained of general neurasthenic symptoms. *Operation:* removal of a Graafian follicle cyst and separation of many adhesions. *Cystitis* developed on the 9th day, the *urine* showing many pus-cells and a considerable number of red blood-cells and epithelial cells; it was acid in reaction and contained a trace of albumin. *Bacteriological examination: B. pyocyaneus.* The treatment in this case was carried on for a longer time than usually required; the trigonum, which was most injected, was touched with 2% nitrate of silver solution; borax and soda irrigations were used, soda, oil of copaiba and urotropin were given by the mouth. *Result:* cured after about 30 days of treatment.

14. H. S. The patient was a very weak and anemic woman (hemoglobin = 51%). *Operation:* hysteromyomectomy for an enormous myomatous uterus; there was much inevitable handling of the bladder during the operation. *Cystitis* developed on the 9th day, with a great many pus-cells, and some red blood-cells and epithelial cells in a *urine* of a high grade of acidity which contained a trace of albumin. *Bacteriological examination: B. typhosus*, shown by cultural peculiarities, positive Widal reaction with serum of a typhoid patient and comparison with stock cultures of typhoid bacillus, and repeated in a second specimen of urine obtained a few days later. *Treatment:* borax and soda irrigations, urotropin (grs. v, t. i. d.) and soda. *Result:* cured. Patient seen 12 months later, when urine was absolutely normal.

15. S. Hemoglobin = 51%. *Operation:* hysteromyomectomy for enormous myomatous uterus with many and dense adhesions. The urine contained a few casts before operation, but no pus cells and no bacteria. The *urine* was repeatedly examined after the operation and for the first 6 days a marked increase in the number of casts was noted. On the 7th day, besides these, a large number of pus-cells were voided, and a number of red blood and epithelial cells; the *urine* was usually acid and contained considerable albumin. The patient had all the symptoms of *cystitis. Bacteriological examination: Staphylococcus pyogenes aureus. Treatment:* soda and salol by mouth; Blaud's pills. *Result:* cured.

16. W. F. S. The patient had had some frequency of micturition due to the pressure of the tumor upon the bladder. *Operation:* removal of densely adherent ovarian papillomata (both sides). *Cystitis:* developed on the 11th day; the *urine* contained many pus, red blood-cells and epithelial cells, and a trace of albumin. Its acidity was extremely high, being 36 (10 = normal acidity). *Bacteriological examination: B. coli communis. Treatment:* urotropin (grs. x, t. i. d. for 17 days) and soda. *Result:* cured (urine had acidity of 10, *i. e.* normal acidity at close of treatment).

17. W. H. S. A very weak, anemic woman (hemoglobin = 33%). *Operation:* removal of extensive papillomata of both ovaries; removal of uterus

(many adhesions); operation extremely long and tedious. *Cystitis* developed on the 20th day. *Urine:* a small number of pus and blood-cells, very *many* bacteria, the condition thus approaching bacteriuria; reaction, acid, the faintest trace of albumin. *Bacteriological examination: Staphylococcus pyogenes albus. Treatment:* soda and urotropin (grs. x, t. i. d.) by mouth, Blaud's pills. *Result:* much improved after a week's treatment; patient still under treatment; (cured).

18 (see 81). W. *Operation:* nephropexy (right) for floating kidney. On the 11th day the patient developed all the symptoms of an acute *cystitis*, and a few days later also some pain in the region of the right kidney. The *urine* contained many pus-cells, some blood-cells and epithelial cells, and a considerable quantity of albumin; the urine was acid. *Bacteriological examination: B. coli communis.* The considerable quantity of albumin suggested that there was also a pyelitis, and the catheterization of the right kidney substantiated this view (see "Acute Pyelitis"). *Treatment:* borax and soda irrigations, urotropin and soda by mouth. *Result:* cured after 24 days of treatment.

19. W. Pelvic inflammatory disease. The patient had numerous and dense pelvic adhesions and was in an extremely poor physical condition. She was given ether and thoroughly examined, and was catheterized several times afterwards. The patient developed *cystitis* 4 days after the examination; the *urine* of acid reaction, showing a considerable number of pus-cells, some epithelial and red blood-cells, and a faint trace of albumin. *Bacteriological examination: B. coli communis. Treatment:* urotropin, soda, copaiba and lithia. *Result:* cured.

20. W. The patient had a large myomatous uterus, cysts of both ovaries and pelvic peritonitis. The hemoglobin was 68%. *Operation:* hystero-myo-salpingo-cysto-oöphorectomy. (The patient, previous to the operation, although the urine was perfectly normal, had increased frequency of micturition, due to the pressure of the tumor on the bladder.) *Cystitis* appeared on the 10th day. *Urine:* small number of pus, red blood and epithelial cells; faint trace of albumin, acid. *Bacteriological examination: B. coli communis* in enormous numbers. The disproportion between the number of bacteria and the number of pus-cells would make one think it probable that this case was one of high grade of bacteriuria plus a cystitis of mild grade. The patient was catheterized but twice in this case. *Treatment:* urotropin (grs. x, t. i. d. for 12 days) and soda. *Result:* cured.

21. Z. *Operation:* hysterectomy and separation of many adhesions. *Cystitis* developed with the usual symptoms, and the *urine* showed many pus-cells, some red blood and epithelial cells, and a trace of albumin; the urine was acid. *Bacteriological examination: B. coli communis.* Notes on treatment mislaid.

22. D. *Operation:* instrumental delivery of very large child, which was associated with considerable trauma. The patient was catheterized several times. *Cystitis* developed within a few days. *Urine:* enormous numbers of pus-cells, some red blood and epithelial cells, trace of

albumin, acid. *Bacteriological examination: B. coli communis. Treatment:* cystogen (grs. v. t. i. d.) and soda by mouth. *Result:* cured in a few weeks' time. Patient seen 8 months later, when urine was perfectly normal.

23. N. *Operation:* instrumental delivery of child; considerable trauma; mother was in extremely precarious state; albumin in urine before delivery and for a considerable time afterwards; many convulsions preceding, during and after delivery. *Cystitis* developed within a few days. *Urine:* enormous numbers of pus-cells, some red blood and epithelial cells, casts, large amount of albumin, acid. *Bacteriological examination: B. coli communis. Treatment:* urotropin and soda by mouth, Blaud's pills. *Result:* cured.

24. H. *Operation:* hystero-salpingo-oöphorectomy for salpingitis, oöphoritis and myomatous uterus; many adhesions. The patient had increased frequency of micturition before the operation, due to pressure of the tumor, but the urine was absolutely normal and a culture showed it to be sterile. *Cystitis* developed on the 15th day. *Urine:* many pus-cells, some red blood-cells and epithelial cells, trace of albumin, acid, many short bacilli, sluggishly motile, resembling morphologically colon bacilli. *Bacteriological examination:* unfortunately no cultures were made from this case; the microorganism, however, was probably the B. coli communis (this case is, of course, not included in the series of colon cases). *Treatment:* urotropin (grs. x, t. i. d.) and soda by mouth for 7 days. *Result:* cured.

25. W. Weak, anemic woman; ill for a long while. *Operation:* incision into large appendicular abscess, which was adherent to the pelvic organs. *Cystitis* developed on the 5th day. *Urine:* acid or neutral, very occasionally alkaline; large number of red blood-cells, considerable number of pus and epithelial cells, small amount of albumin. *Bacteriological examination: Staphylococcus pyogenes aureus. Treatment:* notes on treatment mislaid (presumably urotropin, benzoic acid, Blaud's pills). *Result:* cured in 18 days.

26 (see 82). L. (Patient was a man, but case is added because of its interest bacteriologically.) *Operation:* appendicectomy (done elsewhere 3 weeks before he was seen by us). Patient was catheterized several times during first few days after operation by an orderly. Developed symptoms of *cystitis* of most marked degree on 3d or 4th day, with ammoniacal *urine*, intensely alkaline, many pus-cells, small amount of albumin. A few days later developed also symptoms of pyelitis. *Bacteriological examination: B. proteus vulgaris* (made 3 weeks later). *Treatment:* incision into kidney, drainage, urotropin and benzoic acid by mouth. *Result:* much improved; patient still under treatment; (cured).

Cases of Chronic Cystitis (non-tuberculous).

A. cystitis alone.

27. A. Torn and badly treated at labor 20 years ago, since which time there has been pain in bladder, pain on micturition and frequency,

all of which have steadily increased. For past 3 years life has been practically unbearable and general health very poor. The patient has attacks of frequent urination (every 15 minutes) alternating with periods of retention lasting from 12 to 24 hours. *Cystoscopic examination:* an extremely ulcerated bladder, with an enormous "bas fond." *Urine:* acid, trace of albumin, a great number of pus-cells and bladder epithelial cells. *Bacteriological examination: B. coli communis. Treatment:* lithia, soda by mouth; irrigations of borax and soda, general hygienic treatment. *Result:* improved (patient was under treatment but a short time).

28. A. Trouble started at menopause, 2 months previously, with a feeling of pressure and painful and frequent micturition. Patient was in extremely poor condition at the time. *Cystoscopic examination:* a number of reddish prominences on the trigonum; posterior hemisphere injected with whitish spots and lines over it. *Urine:* acid, trace of albumin, very many pus-cells, occasional epithelial cells. *Bacteriological examination: B. coli communis. Treatment:* 5% silver nitrate solution to ulcerated spots. *Result:* not much improvement (patient only came for 3 treatments).

29. B. Since birth of child, 2 years previously, trouble with bladder, especially frequent micturition; fell and struck herself in lower abdomen 1 year ago, since when there has been constant vesical pain, and the patient has felt a definitely localized painful spot in the bladder. The patient is neurotic and anemic. *Urine:* acid or neutral, some pus-cells and epithelial cells, faint trace of albumin. *Bacteriological examination: Staphylococcus pyogenes aureus. Treatment:* application of 5% solution of silver nitrate to reddened and slightly ulcerated trigonum. *Result:* cured in eight weeks.

30. B. The uterus is in marked retroflexion and the vaginal outlet much relaxed. The vesical trouble developed insidiously, consisting of marked frequency and pain for the past few months. *Cystoscopic examination:* bladder holds but 160 ccm.; trigonum markedly reddened. *Urine:* alkaline, odor of ammonia; many pus-cells, some epithelial cells; trace of albumin, triple phosphate crystals. *Bacteriological examination: slowly-liquefying Staphylococcus pyogenes albus. Treatment:* 5% silver nitrate solution to trigonum. *Result:* patient seen but once.

31. B. For years patient has had attacks of pain before and during micturition, and had been treated by her physician for this with irrigations of borax and soda, local applications and general treatment. Later she passed blood in the urine several times. *Cystoscopic examination:* hyperemia of trigonum, with numerous ulcerated spots of small size; tenderness of bladder (vaginal palpation). *Urine:* some epithelial and many pus-cells, acid, trace of albumin. *Bacteriological examination:* unidentified bacillus, morphologically resembling *B. coil communis*, but, culturally, producing no indol in peptone, nor gas in glucose agar. *Treatment:* application of 5% silver nitrate solution (only once); irrigations of protargol (1%), urotropin (grs. x, t. i. d.). *Result:* markedly improved, ulcerations almost healed, only occasional pus-cells in urine.

32. B. Pelvic inflammatory disease, pelvic new growth (inflammatory?) projecting into bladder; pain and frequency of urination. *Cystoscopic examination:* one large localized ulcer at base of bladder, with red bleeding surface, covered with flakes of pus. *Urine:* acid, trace of albumin, considerable number of red blood-cells, some pus and epithelial cells. *Bacteriological examination:* much attenuated and slowly growing *Staphylococcus pyogenes albus. Treatment:* operation (abdominal) for pelvic inflammatory trouble, excision of ulcer. *Result:* patient convalescing from operation.

33. C. Neurotic woman of 28 years. For 12 years she has complained of frequent micturition, and has been catheterized and treated by many physicians (probably giving rise to the infection). *Cystoscopic examination:* markedly contracted and fearfully ulcerated bladder. *Urine:* enormous numbers of pus-cells, a few red blood-cells and epithelial cells, acid, small amount of albumin. *Bacteriological examination: B. coli communis* in enormous numbers. Patient seen but once and not treated.

34. C. The patient became extremely tired and caught a severe cold 2 years ago, and immediately afterwards complained of frequency of and much pain on urination, the symptoms becoming much more severe after an operation for extra-uterine pregnancy. *Cystoscopic examination:* injected and slightly ulcerated bladder. *Urine:* large numbers of pus-cells, a few red blood and epithelial cells, acid, faint trace of albumin. *Bacteriological examination: B. coli communis.* Patient at present under treatment (borax and soda irrigations, silver nitrate irrigations and local applications, urotropin by mouth). The patient catheterized herself very frequently before coming under observation.

35. F., age 65 years. Eleven years ago the urethra was opened because "the mucous membrane pushed down through the urethral orifice, causing intense pain." Five years later the urethral opening was closed. Since the first operation there has always been pus in the urine, much pain in urethra and bladder, occasional hematuria, frequent voiding of urine, the patient recently never holding more than 60 ccm. *Cystoscopic examination:* stricture of urethra, urethral orifice pouting and deeply injected, contracted; injected and ulcerated bladder. *Urine:* enormous numbers of pus-cells, many red blood and epithelial cells, trace or very small amount of albumin, acid, neutral or occasionally alkaline. *Bacteriological examination: Staphylococcus pyogenes aureus. Treatment:* borax and soda, and silver nitrate irrigations; instillations and local applications of silver nitrate; dilatation of bladder by hydraulic pressure; Blaud's pills. *Result:* (patient still under treatment), marked improvement in every way, bladder now holding 300 ccm. without discomfort, many of the ulcerations healed and the number of pus-cells and microorganisms markedly decreased (the latter from 300 to 25 in a definite amount of urine).

36. G. *Operation:* hystero-myo-salpingo-oöphorectomy one year previously for myomatous, densely adherent uterus. Ever since 1 month after the operation she has been complaining of frequent and painful micturition, cloudy urine and vesical pain. *Urine:* acid, considerable

number of pus-cells and bladder epithelial cells, faint trace of albumin. *Bacteriological examination: B. coli communis.* Not treated now. Formerly treated with boric acid and silver nitrate irrigations.

37. H., 54 years old. Two days before menopause (4 months ago) the patient complained of pain in bladder and frequent desire to urinate. Since then pain and increased frequency, the patient having to urinate 3 to 4 times every night. No bladder symptoms at any time previous to the menopause. *Cystoscopic examination:* general inflammation of vesical mucosa, with very slight ulceration in a few small spots; adhesions about cervix; hematometra. *Urine:* acid, trace of albumin, very many pus-cells, a considerable number of red blood-cells and epithelial cells. *Bacteriological examination: B. coli communis. Treatment:* borax and soda irrigations, silver nitrate irrigations, soda by mouth, dilatation of bladder by hydraulic pressure. *Result:* cured. Bladder, which on admission held but 200 ccm., held at the time of the patient's discharge (30 days later) 570 ccm.

38. J., aged 63 years. Six years ago had a urethral caruncle removed, since which time there has been urinary incontinence (physician evidently removed urethral sphincter), and some pain on urination. The inflammation in the bladder is mostly confined to the neighborhood of the internal urethral orifice. *Urine:* small number of pus-cells, a few epithelial cells, usually acid, faintest trace of albumin. *Bacteriological examination: Staphylococcus pyogenes aureus. Treatment:* plastic operation, formation of new urethra.

39. McK. Two years before the patient had slight pain in the urethra. Her doctor removed a caruncle and later gave irrigations and local treatment, since which time the urethral pain, burning sensation on urination and frequency have been present. *Cystoscopic examination:* bladder injected, especially about internal urethral orifice; urethra injected; bladder contracted (holding but 100 ccm.). *Urine:* acid, trace of albumin, great numbers of pus-cells, some epithelial cells, and few red blood-cells. *Bacteriological examination: B. coli communis. Treatment:* urotropin (grs. x, t. i. d.), soda, lithia water by mouth, irrigations of borax and soda, distention by hydraulic pressure. *Result:* markedly improved (urine markedly cleared up, bladder holding 400 ccm. and all symptoms abated when patient was last heard from; then under treatment at home).

40. M. A very neurotic girl of 23 years, with general enteroptosis. She had always complained of painful and burning micturition, and thus led her physician to give her local applications and irrigate the bladder; later the bladder was opened and drained, this opening finally closing up; this operation was repeated 2 years later. *Cystoscopic examination:* universally deeply injected bladder with a large number of deeply ulcerated areas. *Urine:* acid, trace of albumin, enormous number of pus-cells, many red blood-cells and epithelial cells. *Bacteriological examination: B. coli communis* in enormous quantities (this was the most active colon bacillus seen during my investigations, being a rapid and profuse grower, a rapid producer of gas and indol and quite actively

motile). *Treatment:* urotropin (grs. x. t. i. d.), soda by mouth; instillations, irrigations and local applications of silver nitrate; irrigations of formalin, dilatation of bladder under hydraulic pressure. *Result:* some improvement after several months' treatment (patient still under treatment).

41. P. The patient has a markedly relaxed vaginal outlet and a retroflexed uterus. Her only child was born 13½ years ago. Since the birth of the child the patient has felt the uterus constantly pressing upon the bladder and has had a feeling of insufficient pelvic support. After exerting herself a great deal and being under a great nervous strain, 12½ years ago, she had an acute attack of vesical pain with some hematuria. For the past 10½ years she has had constant vesical pain, frequency of micturition and increasing disability to hold large quantities of urine in the bladder. The patient has been treated by various physicians during this time, receiving various kinds of irrigations and local applications and consequently being catheterized a great number of times, the technique of the latter operation being horrible in many instances, neither the catheter being boiled nor the parts cleansed in many cases. Pyuria, while not present at first, has been present since the beginning of the treatment. The patient has been confined to her bed for 6 months. *Cystoscopic examination:* markedly contracted, intensely injected bladder, with a number of superficial ulcerations, especially on the posterior surface; most markedly ulcerated area at the left cornu; trigonum normal (bladder holds but 50 ccm.). *Urine:* enormous numbers of pus-cells, some red blood-cells and epithelial cells, small amount of albumin, acid. *Bacteriological examination: B. coli communis* in large quantities. *Treatment:* irrigations, instillations and local applications of silver nitrate; soda by mouth; dilatation of bladder under hydraulic pressure; irrigations with formalin; the whole treatment lasting three months. *Result:* cured (urine, normal; cystoscopic examination, bladder normal; bacteriological examination negative; capacity of bladder over 400 ccm.; patient examined 1, 2 and 3 months after she was cured and no recurrence of trouble found).

42. R., age 55 years. Was operated upon 14 years ago for tear of the vagina, the patient being catheterized several times. From that time the patient has suffered with symptoms of cystitis. The patient herself noted that the nurse who attended her at the time of her operation was not careful about her technique. The attack began with an acute attack of vesical pain, lasting one week. Since then the patient has exhibited all the symptoms of a chronic cystitis, becoming gradually worse, with severe pain, marked frequency of micturition, hematuria and pyuria, so that for the past few years life has been almost unbearable, so constant has been the desire to urinate and the pain. She has had a variety of treatments—dilatation of the urethra, resection of the relaxed vaginal outlet, local applications and irrigations of various kinds, and the administration of various substances by mouth, including urotropin, benzoic and boracic acids, the latter of which seemed to be the only substance to give her any relief. *Cystoscopic examination:* markedly contracted bladder, with extensively and deeply ulcerated surface, neck of bladder much inflamed. *Urine:*

alkaline or ammoniacal, trace of albumin, enormous number of pus-cells and epithelial cells, many red blood-cells, triple phosphate crystals. *Bacteriological examination:* slowly liquefying *Staphylococcus pyogenes albus* (7 cultures, 25 urinary examinations made). *Treatment:* boracic acid and urotropin (grs. x, t. i. d.) by mouth, irrigations with silver nitrate, formalin and boracic acid, instillations of silver nitrate, local applications of silver nitrate, dilatation of bladder by hydraulic pressure. *Result: cured* after 2 months' treatment (patient seen 1, 3 and 6 months later and no recurrence). Urine has been acid and sterile, and contains no pus-cells. Bladder holds normal amount.

43. T. Difficult, instrumental labor 3 years ago. Two months later she noticed dribbling of urine, increasing to complete incontinence when patient was on her feet. Prolapse of vaginal wall twice repaired. For the past 8 months there has been constant leakage of urine. *Examination:* bladder not tender but crowded down behind symphysis, outlet relaxed, urethral outlet relaxed, trigonum markedly injected. *Urine:* acid, a moderate number of pus-cells, some red blood and epithelial cells, trace of albumin. *Bacteriological examination: B. coli communis. Treatment:* anterior colporraphy, resection of sphincter urethræ, large amounts of water by mouth and vesical irrigations of borax and soda. *Result:* cured.

44. W. Woman in weak, run-down, anemic condition. *Cystitis* developed insidiously, with slightly increased frequency of micturition and some pain, later increasing but never reaching a high degree. *Urine:* neutral or acid, trace of albumin, many pus cells, some epithelial cells. *Bacteriological examination: Staphylococcus pyogenes albus. Result:* patient seen but once.

45. W. The patient had a relaxed vaginal outlet, and a large cystocele. For some time previously she had had a dull aching in the bladder region with marked urinary frequency and some pain. The urine was never bloody. The patient had frequently catheterized herself and irrigated the bladder. *Urine:* small number of pus-cells before operation, increased markedly for first few days after operation, trace of albumin, some epithelial cells, acid. *Bacteriological examination: B. coli communis. Treatment:* resection of relaxed vaginal outlet, anterior colporraphy, vesical irrigations of borax and soda, dilatation of bladder by hydraulic pressure. *Result:* cured (patient's bladder, which held 65 ccm. on admission, on discharge held 550 ccm).

46 (see 58). E. For many years patient suffered with frequent and very painful micturition, the condition developing insidiously. *Examination* showed a markedly contracted bladder with many typical tuberculous ulcerations and tubercle bacilli in the urine. Irrigations, local applications and curettage proving of little avail; a suprapubic opening was made into the bladder and the patient placed in a tub of constantly flowing water so that there would be constant vesical irrigation. Subsequently the bladder became infected with the *B. coli communis*, so that this microorganism and the *tubercle bacillus* are now found together in the bladder. The urine is markedly acid, contains enormous numbers of pus-cells, some red blood and epithelial cells, and a trace of albumin.

47. C. The patient for a long period of time had complained of vesical pain and urinary frequency. The *urine* was acid, contained a large number of pus-cells, some red blood and epithelial cells and a trace of albumin. No *bacteriological examination* was made (case not seen by the author). *Cystoscopic examination:* large single ulcer in base of bladder. *Treatment:* as local applications seemed to be of little service, the relaxed vaginal outlet was resected; when under the same local treatment (silver nitrate) the condition rapidly cleared up, the urine becoming normal, containing neither pus-cells nor blood-cells, and the bacteriological examination being negative.

48. F. Neurasthenical woman, trigonitis and irritable bladder for some time. Upper urethra and bladder deeply injected. *Urine:* a few leucocytes, acid, no albumin. Later the patient developed a vesico-vaginal fistula and a cystitis with high grade of pyuria, and acid urine (cultures not taken; case not seen by author). *Treatment:* resection of relaxed vaginal outlet, closure of fistula (2 inches long, behind internal urethral orifice. Subsequently *urine* contained only an occasional pus-cell, was acid, and the *bacteriological examination* was negative. The patient, however, still complains of irritable bladder and too frequent micturition and is as neurasthenical as ever.

49. McD. The patient had a severe fall some time previously from her bicycle, falling upon the hypogastrium. Since then she has complained of frequent and painful urination, urinating every 1 to 3 hours during the day, and getting up once at night. *Examination:* area of ulceration at vertex of bladder, deeply injected and covered with a layer of bloody pus; trigonum injected. *Uterus* in marked retroversion. *Urine:* acid, no albumin, a few pus-cells, red blood-cells and epithelial cells. *Bacteriological examination:* no cultures grew on ordinary media; no organisms seen in dried and stained specimens of sediment; no Tubercle bacilli found. *Treatment:* excision of ulcerated area by a coeliotomy; bladder irrigations with borax and soda solution. *Result:* there was considerable pyuria for a number of days after the operation, but no microorganisms grew on the various media, nor were any found in stained specimens of the sediment. The urine cleared up entirely (except for an occasional pus-cell) in 7 weeks. The patient, seen several months subsequently, was perfectly well and the urine normal.

50. Q. The patient had a pan-hysterectomy performed 4 years previously for myomatous uterus, double hydrosalpinx and dermoid cyst of ovary. For 3 years she felt perfectly well, and then, without apparent cause, except the fatigue caused by doing her usual duties during a period of hot weather, developed a severe attack of nervous prostration, with some pain in head and flanks. This was shortly followed by a tendency towards increased frequency of micturition but no pain, the patient getting up 3 to 4 times during the night; the urination was painless, however. This condition has persisted ever since. A *diagnosis of cystitis* was made from the cystoscopic examination, but no notes of the exact vesical lesions are to be found. *Urine:* acid, trace of albumin, many pus-cells and epithelial cells, a few red blood-cells, specific gravity 1.017. *Bacteriological examination:* no microorganisms grew upon the

ordinary media; none were found on stained specimens of the dried sediment; no Tubercle bacilli were found. *Treatment:* urotropin and soda by mouth, bladder irrigations of formalin (1: 1000) and borax and soda. *Result:* in less than a month the symptoms had entirely disappeared, but the urine still contained a few pus-cells; cultures were still sterile.

Cases of Chronic Cystitis (non-tuberculous).

B. associated with pyelitis and pyelonephritis.

(For renal portion of these histories, see under "*Chronic pyelitis.*")

51 (see 91). M. After an attack of influenza one year ago, developed an illness pronounced "typhoid fever," with temperature reaching 105° F. The patient, however, had also all the symptoms of an acute cystitis—very painful and frequent micturition, etc. Since then she has had symptoms of cystitis off and on up to the present time, much better of late under hygienic treatment and administration of large quantities of water by mouth. *Cystoscopic examination:* reddening about trigonum but not enough to account for the grade of pyuria. *Urine examination:* many pus-cells, a few epithelial cells, acid, considerable albumin. *Bacteriological examination: B. coli communis. Treatment:* urotropin (grs. x, t. i. d.), soda and large quantities of water by mouth; Blaud's pills. *Result: improved.*

52 (see 92). R. Four years ago, when the patient was very anemic and run down (hemoglobin = 50%), she suddenly developed a sharp attack of pain in the bladder, with frequent and painful micturition, which has continued up to the present time; 2 years ago developed symptoms of a right pyelitis. *Cystoscopic examination:* reddening about the right ureteral orifice; some general reddening. *Urine:* enormous number of pus-cells, moderate amount of or considerable albumin, a few epithelial cells, usually neutral or alkaline, occasionally acid. *Bacteriological examination: B. proteus vulgaris* (Hauser). *Treatment:* incision into kidney, removal of stone, irrigation and drainage (bladder had been treated at home for quite a time), Blaud's pills. *Result:* much improved.

53 (see 93). R. Five years ago the patient, a young, nervous girl, was much overworked and in poor general health. She developed a little "ardor urinæ," and was treated locally for this. She immediately developed all the symptoms of cystitis, extreme pain and frequency, etc. She has had all kinds of local treatment, irrigations with formalin, etc.; dilatation of the urethral sphincter, etc., since then. The condition has gotten steadily worse, so that now life is practically unbearable, the pain is almost constant and the patient urinates every few minutes. One year ago she developed the symptoms of a left pyelitis. *Cystoscopic examination:* bladder extremely contracted (never holds more than 15 ccm.), with extreme reddening and extensive ulcerations. *Urine:* enormous numbers of pus-cells, some red blood and epithelial cells, acid, considerable albumin. *Bacteriological examination: B. coli communis. Treatment:* hygienic treatment, curettage of bladder, nephrotomy and washing out of left renal pelvis, suprapubic cystotomy, drainage by

immersion of patient in tub of constantly flowing water, dilatation of bladder by hydraulic pressure. *Result:* markedly improved, bladder now holds 105 ccm., urine contains but a few pus-cells, bacteria markedly diminished (now only 15 in 3 loops; at first over 400). [Later L. nephrectomy.]

54 (see 87). Bl. The patient, a poorly nourished woman of pasty complexion, was taken with severe burning pain in the bladder, painful and frequent micturition 8 months ago and was in bed 3 weeks with these symptoms. At the end of this attack she developed severe pain in the region of the right kidney. Only slight pain up to 10 days before she was seen, when she had a second attack of pain on micturition in bladder and in right side with some hematuria; the patient has noted that the urine often contains a brick-dust sediment. *Cystoscopic examination:* trigonum injected, with a few small superficial ulcerations. *Urine:* acid, small amount of albumin, small number of white and red blood-cells. *Bacteriological examination: B. coli communis. Treatment:* resection of right kidney for multiple abscesses in the cortex. *Result:* still under treatment.

55 (see 88). C. Symptoms of calculous pyelitis (left) for 15 years, with pyuria, loss of strength and weight. Six years ago it was noted that the bladder was extremely sensitive about ureteral orifices. Some pain in region of right kidney for past few years. Large left pus kidney and calculus (1 pint of pus) removed 3 years ago. *Cystoscopic examination:* trigonum deeply injected, with little puriform deposits in various spots. *Urine:* many pus-cells, some red blood-cells, usually alkaline, occasionally neutral or (once or twice) slightly acid, extremely pale and low specific gravity, moderate amount of albumin. *Bacteriological examination:* slowly liquefying *Staphylococcus pyogenes albus. Treatment:* general hygienic treatment, with drinking of large quantities of water and occasional irrigations of bladder and right renal pelvis. *Result:* patient is holding her own and is able to do considerable work.

56 (see 89). D. Renal calculus and pyelitis (right) of 3 years' duration. Slightly increased urination of late. *Cystoscopic examination:* slight reddening of trigonum and puffiness about right ureteral orifice. *Bacteriological examination:* slowly liquefying *Staphylococcus pyogenes albus* (slight cystitis secondary to pyelitis). *Urine:* alkaline or neutral, occasionally slightly acid, with many pus-cells and considerable albumin.

57 (see 90). G. The patient has for several years complained of slightly increased frequency of micturition, a minimal amount of pain on urination and very cloudy urine. She had been treated for a long time with vesical irrigations and medicines by mouth without any apparent improvement in the condition of the urine, the symptoms themselves being so mild as to require no treatment. The bladder on examination was found to be practically normal, except a slight reddening about the trigonum and the left ureteral opening. *Urine:* acid, enormous numbers of pus-cells, less specific gravity, considerable albumin. *Bacteriological examination: B. coli communis.*

Cases of Tuberculous Cystitis.

A. cystitis alone.

58 (see 46). E. History of cystitis for many years, with frequent, painful micturition, hematuria, etc. *Cystoscopic examination:* markedly contracted bladder with many typical tuberculous ulcerations. *Urine:* many pus and red blood-cells, epithelial cells, acid, trace of albumin. *Bacteriological examination:* no growth on ordinary media; *Tubercle bacilli* found in considerable number. *Treatment:* the usual local and general treatment proving unavailing, a suprapubic incision was made into the bladder and continuous irrigation brought about by immersion of patient in a tub of constantly flowing water. Later *B. coli communis* was found in the urine. *Result:* not much change.

59. S. The patient had a tuberculous family history. Three years before she was operated upon for renal calculus and pyelonephrosis. The history of this condition was as follows: 6 years before the operation she had been seized with sudden pain in the right side, high fever and scanty urination, being ill 3 weeks. One year later there was a 2d attack, and since these attacks every 3 or 4 weeks, recently with hot flushes and night-sweats, with cough for 5 or 6 weeks preceding the operation; after voiding, pain in the neck of the bladder; the patient gets up once or twice at night to urinate. The *operation* was an incision into an enormously dilated right kidney, evacuation of a large amount of pus and of a stone, of pigeon's-egg size, from the renal pelvis, thorough washing out of the kidney and drainage. Three years later the patient was seen again; she had then all the symptoms of cystitis. The *urine* contained an enormous number of pus-cells, some red blood-cells and epithelial cells and was acid. *Bacteriological examination:* no microorganisms grew on the usual media, but a few *Tubercle bacilli* were found after long and careful search. Whether the pyelonephrosis in this case was of tuberculous origin or not, it is impossible to say, as the ureter was not catheterized nor was the renal pus examined for Tubercle bacilli at the time of operation. This case, therefore, perhaps belongs to the following group.

Cases of Tuberculous Cystitis.

B. associated with pyelitis and pyelonephritis.

(For renal portion of these histories, see under "Chronic tuberculous pyelitis.")

60 (see 97). L. Long, vague history of painful, frequent micturition with pyuria and some hematuria occasionally, and also subsequently pain in left flank. *Examination:* tuberculous ulceration of bladder, especially about left ureteral opening; hyperemia of bladder; thickening of left ureter. *Urine:* many pus-cells, some epithelial and red blood-cells, acid, considerable albumin. *Bacteriological examination:* sterile on ordinary media; *Tubercle bacilli* in small numbers.

61 (see 98). McH. Two years ago painful and frequent micturition, which has been steadily increasing ever since; with cloudy and sometimes bloody urine. Sometimes after the initial symptoms, the patient

complained of pain in the right side, which has been constant ever since. Considerable loss of weight, some feverishness at night, general loss of strength. *Urine:* enormous numbers of pus-cells, many blood-cells and epithelial cells, acid, much albumin. *Examination:* markedly contracted, extremely hyperemic, much ulcerated bladder, the ulcerations being especially marked in the area about the left uretral opening. Left ureter much thickened. *Bacteriological examination:* no growth on ordinary media; *Tubercle bacilli* in great numbers.

62 (see 99). McC. The condition developed 2 years ago with typical symptoms of cystitis, painful and frequent micturition, pyuria and occasionally hematuria and slight fever. These symptoms have been present from then to the present time, although gradually diminishing in intensity, so that now the bladder symptoms are very slight. For the past 5 months there has been a constant pain in the left side. *Cystoscopic examination:* some hyperemia about left ureter. *Urine:* many pus-cells, some red blood-cells and epithelial cells, acid, considerable albumin. *Bacteriological examination:* sterile on ordinary media; *Tubercle bacilli* in small number.

63 (see 100). P. Three months ago she complained of pain in the bladder and frequency of micturition, gradually getting worse; subsequently several attacks of hematuria. *Cystoscopic examination:* whole vault of bladder converted into a red, irregular mass with pus in the interstices; left ureteral orifice is the centre of a flat, irregular tuberculous mass, with pus in its centre; left ureter is a dense, hard cord. Patient has lost much weight and strength. *Urine:* acid, considerable albumin, many pus-cells and red blood-cells, a considerable number of epithelial cells. *Bacteriological examination:* sterile on ordinary media; *Tubercle bacilli* in small number. The patient is a pale, poorly nourished seamstress, but *no* tuberculous family history was to be discovered.

Cases with Symptoms of Cystitis but no Infection.

A. Those due to hyperacidity of the urine.

64. C. Hysterical young woman, extremely nervous, teaches school and has to be on her feet most of the time, condition persisting for 3 years, always gets markedly better during her vacation. *Symptoms:* at first only frequent desire to urinate, later (for past year) pain and burning sensation in bladder. Symptoms are exaggerated by cold, overexertion and nervous strain. *Examination:* trigonum deeply injected; right floating kidney. *Urine:* a few pus-cells and epithelial cells, no albumin, extremely acid (acidity = 27.5). *Bacteriological examination:* sterile. *Treatment:* alkalies by mouth; hygienic; rest cure. *Result:* cured. Patient seen 6 months later. Has no trouble of this nature; whenever any tendency towards frequent urination, takes alkalies by mouth and rests as far as possible and condition is relieved.

65. D. Neurasthenical woman of twenty-eight, with many hysterical manifestations. *Symptoms:* scalding and frequent urination for past 6 to 7 years with pain in bladder. *Examination:* intense hyperemia of trigonum and upper urethra. *Urine:* a few pus-cells and epithelial cells,

occasional red blood-cells, no albumin, very acid (acidity = 30.0). *Bacteriological examination:* sterile. *Treatment:* alkalies by mouth, cold packs, hygienic rest cure, scarification of trigonum.

66. D. Intensely neurasthenical young married woman, with myomatous uterus, retroflexion of uterus, right floating kidney, and mucous gastritis with hypochlorhydria. *Bladder* showed intense reddening of trigonum. Urination was frequent and somewhat painful (in mouth of urethra). *Urine:* a small number of pus-cells, no albumin, very acid (acidity = 20), specific gravity = 1.005, very pale in color, *sterile. Treatment:* myomectomy, suspension of uterus, double salpingectomy; subsequently hygienic, alkalies by mouth. *Result:* symptoms entirely disappeared for more than 6 months, when the patient attempted to do too much and the symptoms and hyperacidity returned. She was given the rest cure with alkalies by mouth and the symptoms again disappeared.

67. H. Nervous woman of thirty-one, complaining of nervousness, headache and pain in the back of the neck, and painful, frequent micturition (urinates 4 to 5 times at night), and irritable bladder. *Examination:* hyperemia of trigonum. *Urine:* a few pus-cells, no albumin, very acid (acidity = 31.00); *sterile.*

68. L. *Complaint:* irritable bladder and frequency of micturition. *Examination:* injected trigonum. *Urine:* occasional pus-cell, no albumin, very acid (acidity = 30.0), *sterile.*

69. T. Married woman of twenty-five, very neurotic. Three years ago, six days after marriage complained of frequency of urination and later also of a tender spot in the bladder and dysuria. These symptoms have continued since then and the patient has had the urethral sphincter dilated, the tender spot touched with various substances, and the bladder washed out. *Examination:* intense scarlet injection of the trigonum, especially on left side. *Urine:* a moderate number of pus-cells, occasional red blood-cell, no albumin, intensely acid (acidity = 49.0), *sterile. Treatment:* general hygienic, touching spot with silver nitrate, alkalies by mouth (it requires 110 grains of potassium bicarbonate and potassium citrate per day to render the urine neutral or alkaline). *Result:* marked improvement (patient still under treatment).

70. W. Married woman of thirty-three. Severe instrumental delivery 3 years previously, since which time she has frequently used the catheter to withdraw her urine. During this time she has considerable pain on urination, increased by cold, with a severe attack of vesical pain with fever 2 years ago. *Examination:* deep injection with some ulceration at vertex of bladder. *Urine:* very occasional pus-cells, no albumin, very acid (acidity = 21.0), *sterile.*

71 and 72. Office patients, seen but once, each complaining of frequent and somewhat burning micturition, and in each of whom *cystoscopic examination* revealed a deeply injected trigonum. *Urine:* a few pus-cells, no albumin, very acid (acidity of 71 = 31.0; acidity of 72 = 29.0), *sterile.*

CASES WITH SYMPTOMS OF CYSTITIS BUT WITH NO INFECTION.

B. THOSE DUE TO OTHER CAUSES.

73. A. *Complaint:* frequency of micturition and feeling of lack of support in lower abdomen. *Urine:* slightly acid, no albumin, occasional epithelial cell, *sterile. Examination:* marked relaxation of vaginal outlet.

74. H. *Complaint:* pain in lower abdomen, frequent and somewhat painful micturition. *Urine:* acid, no albumin, a few epithelial and occasional pus-cells, *sterile. Examination:* dense adhesions between uterus, tubes, ovaries and bladder due to old inflammatory trouble.

75. L. *Complaint:* frequent, slightly painful micturition. *Urine:* acid, no albumin, occasional epithelial cell; *sterile. Examination:* relaxed vaginal outlet, retroflexed uterus. *Treatment:* resection of relaxed vaginal outlet, suspension of uterus. *Result:* cured.

76. P. An extremely neurotic young girl of twenty-four. Six years previously, after being caught in a snowstorm, complained of frequent micturition and has been treated for this in all manner of ways ever since. Later there was considerable vesical pain, localized in one spot; also burning sensation over neck of bladder; she urinates 3 to 4 times at night. Condition relieved 3 years ago by an Alexander's operation, but recurred after another surgeon insisted upon excising Skene's glands and has continued unabated ever since. Profuse leucorrheal discharge. *Examination:* rose-red, injected and puffy trigonum, adjacent to which is a small glazed area, where patient localizes her pain. *Urine:* amber clear, no albumin, occasional pus-cell, acid (acidity not tested quantitatively); *sterile.*

77. R. *Complaint:* scalding, frequent micturition, often urinates several times an hour. *Urine:* acid, no albumin, occasional epithelial cell; *sterile. Examination:* mucous polyp protruding from vagina. *Treatment:* removal of polyp by traction. *Result:* cured.

78. S. *Complaint:* frequent micturition and headache. *Urine:* acid, occasional pus-cell, no albumin; *sterile. Examination:* enormous retroflexed uterus.

79. V. *Complaint:* attacks of frequent, slightly painful micturition, coming on without apparent cause and associated with a pricking sensation in the bladder. *Urine:* normal between attacks; during attacks considerable numbers of red blood-cells; *sterile. Examination:* varicosity of vessels in posterior portion of bladder mucosa.

80. W. *Complaint:* very frequent urination, associated with slight pain. *Urine:* acid, no pus-cells, no albumin; *sterile. Examination:* large myomatous uterus, filling the pelvis and pressing upon all the other pelvic organs.

CASES OF ACUTE PYELITIS AND PYELONEPHRITIS.

81 (see 18). W. Extremely anemic woman, thin, weak and emaciated. *Operation:* nephropexy for right floating kidney. On the 11th day

symptoms of acute cystitis, and a few days later also some pain in the right flank. *Urine from bladder:* acid, traces of albumin at first, later a moderate amount, many pus-cells, some epithelial cells and red blood-cells, *B. coli communis*; from *right kidney:* a considerable number of pus-cells, small amount of albumin, acid, *B. coli communis*; from *left kidney:* acid, no albumin, no pus-cells, *sterile*. *Treatment:* bladder irrigation daily with borax and soda solution, soda and urotropin (grs. x, t. i. d.) by mouth, Blaud's pills, hygienic treatment, much water by mouth. *Result:* cured in 35 days.

82 (see 26). L. (This patient is the only man in the series, but the case is added because of its interest.) *Operation:* appendicectomy for chronic recurring appendicitis (operation performed 3 weeks before the patient was seen by Dr. Kelly). Patient was catheterized several times by an orderly during the first 4 days. Developed the symptoms of an acute *cystitis* with ammoniacal urine and many pus-cells, and a week later commenced to complain of pain in the region of the left kidney, with one violent attack of pain, simulating renal colic. *Urine:* intensely alkaline, ammoniacal odor, considerable number of pus-cells, epithelial cells, enormous number of ammonium magnesium phosphate and ammonium urate crystals. *Bacteriological examination: B. proteus vulgaris* from pus in pelvis of kidney, obtained at time of operation. *Treatment:* opening of pelvis of left kidney, irrigation and drainage; benzoic acid and urotropin. Patient still under observation; urine is now acid and contains very few pus-cells and a few bacteria. [Cured.]

Cases of Chronic Pyelitis and Pyelonephritis (non-tuberculous).

A. Alone.

83. B. The condition came on insidiously without any apparent cause. After several typical attacks of renal colic several years ago, a stone was removed from the right kidney (several years before patient was seen by us). Pyuria, pain in right flank, malaise, sometimes attacks of feverishness and nausea ever since then. *Cystoscopic examination:* bladder normal. *Urine:* from *bladder*, slightly alkaline, neutral or slightly acid, specific gravity 1.003-1.011, considerable albumin, many pus-cells, *B. proteus vulgaris*; from *right kidney*, alkaline, considerable albumin, specific gravity 1.003-1.004, many pus-cells, rate of voiding 7 ccm. per minute from right kidney, urea = .004 (urea at same time from urine from bladder = .009), *B. proteus vulgaris*; from *left kidney*, acid, no albumin, no pus-cells, *sterile*. Total amount of urine voided during 24 hours, 2000 to 2400 ccm. *Chemical analysis* of calculus from right kidney: phosphate and carbonate of magnesium and calcium. *Treatment:* hygienic, much water by mouth, urotropin, occasional irrigations of renal pelvis by means of a renal catheter. *Result:* patient by these means manages to keep fairly comfortable.

84. C. The patient herself has been subject to gout for many years; her mother and 2 sisters also had gout. Two years ago she had an acute attack of pain in the right side, with nausea, vomiting, chill and fever; six months later a second attack, and since then frequent attacks of the same nature, all requiring morphia; has never passed any frag-

ments of stone. Just before the attacks begin the urine diminishes in quantity, and the patient becomes dull, heavy and has a tendency to constipation. *Cystoscopic examination:* bladder normal. *Urine:* from *bladder*, acid, large numbers of pus-cells, considerable albumin, specific gravity usually about 1.008, *B. coli communis*; from *right kidney*, acid, enormous numbers of pus-cells, considerable albumin, specific gravity 1.004 (when urine from bladder was 1.008), urea = .004 (urea in urine from bladder = .008), *B. coli communis*, injection of hydrochloric acid solution (1: 500) into pelvis of right kidney through the ureteral catheter, negative; from *left kidney*, acid, no albumin, no pus-cells, *sterile*. Total quantity voided during 24 hours usually about 2100 ccm. *Treatment:* exploratory operation advised but refused; urotropin, large quantities of water and soda by mouth, occasional irrigations of renal pelvis. *Result:* patient's condition remained about the same. *Note.*—Operated upon 6 months later; large pyonephrotic abscess opened and drained; no calculi found.

85. E. The patient had a severe instrumental delivery 1 year previously; the child was extremely large and was killed during delivery. Five days later the urine was partly voided per vaginam and examination showed a large uretero-vaginal fistula on the right side. Many attempts have been made to close this, but so far without success. *Urine:* from *right kidney*, acid, considerable albumin, many pus cells, *B. coli communis*. *Chemical analysis* of small stone passed from the right kidney through the fistula: *uric acid* and *urates*. Besides this constant dribbling of urine, the patient voids normal urine from the bladder in the normal way.

86. R. The patient has had 5 children, the youngest 1 year ago. The patient gives a most unsatisfactory history, but evidently has had pain in the back and right side for the past few years, with loss of weight and strength, and sometimes scanty, but never painful or frequent, urination. *Urine:* from *right kidney* alkaline, many pus-cells, considerable albumin, *B. proteus vulgaris*; from *left kidney*, normal, acid. *Operation:* nephrotomy and removal of calculus; drainage. *Chemical analysis of stone:* phosphate and carbonate of calcium and magnesium.

Cases of Chronic Pyelitis and Pyelonephritis (non-tuberculous).

B. associated with cystitis.

87 (see 54). Bl. Patient, just after marriage, while in a depleted condition, developed the typical symptoms of an acute cystitis, urinating 5 or 6 times at night, the attack necessitating her staying in bed 3 weeks before the symptoms improved; she commenced then, however, to complain of pain in her right flank in the renal region; for 10 days before she was examined she had been suffering from a second attack of vesical pain with some hematuria on one occasion. *Bladder* showed injected trigonum with a few small superficial ulcerations. *Right kidney* was in descensus (3d degree). *Urine:* acid, small amount of albumin, moderate number of pus-cells, a few epithelial cells, *B. coli communis*. Ureter was not catheterized at this time, but subsequently it was, when the infection was found to affect also the right kidney but not the left. *Operation:* resection of right kidney for multiple abscesses in cortex.

88 (see 55). C. The patient for over 15 years has suffered with pyuria and pain, first in the left side, subsequently also in the right, with loss of weight and strength. Four years ago the left kidney was removed and found to be pyelonephrotic and also to contain a calculus. Since then she has been better, but has had slight, though constant, pain in the right side, with slightly painful and somewhat frequent micturition. The *bladder* shows an infection about the left ureteral orifice. *Urine:* from *left kidney*, alkaline or neutral, many pus-cells, considerable number of red blood-cells, considerable albumin, slowly-liquefying *Staphylococcus pyogenes albus.* The kidney is decidedly anterior, in slight descensus and is somewhat tender to pressure. The patient passed a few small calculi from the kidney. *Chemical analysis:* phosphates and carbonates of calcium and magnesium. *Treatment:* urotropin and boric acid by mouth, hygienic.

89 (see 56). D. Five months after a difficult instrumental labor (3½ years ago), patient complained of severe pain in the right side in region of kidney, where she has had dull pain ever since with occasional attacks of sharper pain, exertion and constipation apparently being the most common causes of these exacerbations. The patient had never been catheterized before the development of the trouble, and there is no history of trauma. The *bladder* shows some trigonal reddening and puffiness about the right ureteral orifice. *Urine:* from *right kidney*, alkaline, large numbers of pus-cells, considerable albumin, epithelial cells, slowly-liquefying *Staphylococcus pyogenes albus:* from *left kidney*, acid, no pus-cells, no albumin, *sterile. Treatment:* nephrotomy, removal of calculus and drainage of right kidney; subsequently urotropin and boric acid by mouth, large amounts of water by mouth; hygienic. *Chemical analysis of stone:* phosphates and carbonates of calcium and magnesium. *Result:* patient is much improved; still some pus and bacteria in the urine.

90 (see 57). G. The only thing the patient has complained of has been the passage of cloudy urine with slightly increased urinary frequency for the past few years. For this she has been treated with all sorts of vesical irrigations. The *bladder* was perfectly normal except for some injection of the trigonum and about the left ureteral orifice. *Urine:* from *bladder*, acid, large amount of albumin, large numbers of pus-cells, *B. coli communis*; from *left kidney*, acid, large amount of albumin, large number of pus-cells, *B. coli communis*; from *right kidney*, acid, no pus-cells, no albumin, *sterile. Treatment:* discontinuance of bladder irrigations; general hygienic treatment.

91 (see 51). M. After an attack of influenza 1 year previously developed what was pronounced typhoid fever, but which had associated with it what, from its symptoms, was evidently an acute cystitis, as every symptom was present in a marked degree. Later the vesical condition improved, but she complained of pain in the region of the left kidney. At the time of examination the vesical symptoms were very slight and the bladder only showed a slightly reddened trigonum. *Urine:* from *left kidney*, great numbers of pus-cells, acid, considerable albumin, *B. coli communis*; from *right kidney*, acid, no albumin, no pus-cells, *sterile. Treatment:* general hygienic.

92 (see 52). R. Four years ago, when in extremely poor condition (hemoglobin = 50%), she developed an attack of acute cystitis of marked severity, and 2 years later commenced to complain of severe pain in the right side, for which an appendicectomy was done, but without relief to her symptoms. The bladder symptoms have persisted from the first, although gradually diminishing in severity. *Urine:* from *right kidney*, large numbers of pus-cells, moderate amount of albumin, alkaline, *B. proteus vulgaris*; from *left kidney*, acid, no albumin, no pus-cells, *sterile*. Twenty ccm. of hydrochloric acid (1/5%) were injected into the right renal pelvis and retained 15 minutes; on being analyzed after removal it was found that the fluid contained considerably more calcium and magnesium than the corresponding quantity of urine, showing that there was probably an alkaline stone in the right renal pelvis. *Treatment:* nephrotomy, removal of large calculus, drainage. *Stone, chemical analysis:* carbonate and phosphate of calcium and magnesium; *culture* from centre of *stone*, *B. proteus vulgaris*.

93 (see 53). R. Five years ago, when in an extremely nervous condition, developed a little ardor urinæ and frequency of micturition; was treated for this by local applications, etc., and developed a typical cystitis, which has continued ever since, the symptoms becoming progressively worse. She has had a great variety of treatments for the condition but without avail. One year ago she also developed pain in the left kidney. The bladder showed upon examination all the signs of a chronic cystitis of the worst type with marked contraction and ulceration. *Urine:* from *left kidney*, acid, considerable albumin, large numbers of pus-cells, *B. coli communis*; from *right kidney*, acid, no pus-cells, no albumin, *sterile*. *Treatment:* curettage of bladder, suprapubic incision and drainage, nephrotomy (left), drainage of kidney. *Result:* markedly improved. [Subsequently nephrectomy.]

94. F. The patient, thirty years ago, immediately after a severe instrumental labor, developed all the symptoms of an acute cystitis. The urine was distinctly alkaline, sometimes ammoniacal, and contained large numbers of pus, epithelial and red blood-cells. Twenty years ago she passed a small renal calculus, with considerable hematuria. Shortly after the attack of cystitis she developed pain in the left kidney, which has continued ever since, though now much less than formerly. For the past 20 years the urine has been usually acid. Now passes at frequent intervals enormous quantities of pus, as if from a large sac. *Bladder:* normal, except for a deeply injected, red, puffy area about the right ureteral orifice. *Urine:* from *bladder:* acid, large numbers of pus-cells, considerable albumin, *sterile*; no *Tubercle bacilli* found on most careful search; from *left kidney*, acid, many pus-cells, considerable albumin, *sterile*; from *right kidney*, acid, no pus-cells, no albumin, *sterile*. *Treatment:* nephrotomy, removal of calculus, drainage of large pyonephrotic abscess cavity (culture from abscess: sterile; no Tubercle bacilli). *Stone:* calcium and magnesium phosphates and carbonates. This case is evidently a cystitis followed by a pyelitis due to a microorganism which finally died out.

Tuberculous Pyelitis and Pyelonephritis.

A. alone.

95. B. The patient, of good family history, had been seen for other reasons, 2 months previously and then the urine was absolutely normal, there being no pus or albumin, and no symptoms referable to the urinary tract. The patient, one week before being seen, was taken with all the symptoms of an acute nephritis, nausea and vomiting, much oedema of the legs, puffiness of the face and the passage of very small amounts of smoky, dark-colored urine. The condition seemed a typical acute nephritis, but the slight pyuria associated with it led us to examine the urine bacteriologically. The *bladder* to cystoscopic examination was absolutely normal. *Urine:* from *bladder*, acid, large amount of albumin, casts of all kinds (blood, hyaline, granular and epithelial), many red blood-cells, a considerable number of pus-cells, *sterile* on ordinary media, *Tubercle bacilli* on careful search; from *left kidney*, acid, large amount of albumin, casts of all kinds, many red blood-cells, a considerable number of pus-cells, *sterile* on the ordinary media, *Tubercle bacilli*; from *right kidney*, acid, no albumin, no casts, no pus or blood-cells, *sterile*, no *Tubercle bacilli*. The patient refused to be operated upon, as she suffered no pain whatsoever and was under observation but a short time, during which her oedema, etc., markedly improved under the treatment usually employed in acute nephritis. No signs of tuberculosis elsewhere.

96. S. Ten years ago the patient had an attack of apical tuberculosis (Tubercle bacilli found in sputum, hemoptysis), which was entirely cured by residence in the Adirondack Mountains. Eight months ago the patient had an attack of hematuria, but without pain. *Bladder* was perfectly normal; no ureteral thickening. *Urine:* from *bladder*, acid, considerable albumin, many pus-cells and red blood-cells, *sterile* on ordinary media, Tubercle bacilli in very small numbers; from *left kidney*, acid, considerable albumin, many pus and red blood-cells, *sterile* on ordinary media, Tubercle bacilli (microscopically and by guinea-pig); from *right kidney*, acid, no albumin, no pus or red blood-cells, *sterile*, no *Tubercle bacilli* (microscopically and by guinea-pig). *Treatment:* nephrectomy (left). *Result:* cured.

Tuberculous Pyelitis and Pyelonephritis.

B. associated with cystitis.

97 (see 60). L. Long, vague history of frequent micturition with some pain in bladder and left flank. *Bladder* showed marked reddening and some ulceration about left ureteral orifice; *left ureter* much thickened. *Urine:* from *bladder*, much pus, acid, considerable albumin, epithelial and a few blood-cells, *sterile* on ordinary media, *Tubercle bacilli* in small numbers; from *left kidney*, many pus-cells, some red blood-cells, acid, considerable albumin, *sterile* on ordinary media, *Tubercle bacilli* in small numbers. No evidences of tuberculosis elsewhere.

98 (see 61). McH. For 2 years symptoms of cystitis, gradually increasing in severity, with cloudy, sometimes bloody urine. Subse-

quently pain in right side, which has also gotten worse. *Bladder* is intensely injected and much ulcerated about left ureteral orifice; *left ureter* markedly thickened. *Urine:* from *bladder*, acid, considerable albumin, many pus, red blood and epithelial cells, *sterile* on ordinary media, *Tubercle bacilli* in considerable number; from *right kidney*, acid, considerable albumin, many pus and red blood-cells, *sterile* on ordinary media, *Tubercle bacilli* in considerable number; from *left kidney*, acid, no albumin, no pus or red blood-cells, *sterile*, no *Tubercle bacilli*. *Treatment:* removal of right kidney, ureter and ulcerated portion of bladder. *Result:* death in 3 weeks. No evidences of tuberculosis elsewhere.

99 (see 62). McC. Two years ago developed a typical attack of acute cystitis without any apparent cause, the symptoms of which have continued up to the present time, gradually diminishing in severity. Five months ago she also complained of severe pain in the left renal region, running thence along the ureter into the bladder. The *bladder* now shows only marked reddening about the left ureteral opening; the *ureter* is not much thickened. *Urine:* from *bladder*, acid, considerable albumin, many pus-cells, a few red blood and epithelial cells, *sterile* on ordinary media, *Tubercle bacilli* in moderate number; from *left kidney*, acid, considerable albumin, many pus-cells, some red blood-cells, *sterile* on ordinary media, *Tubercle bacilli*; from *right kidney*, acid, no albumin, no pus or red blood-cells, *sterile*, no *Tubercle bacilli*. *Treatment:* nephrectomy (left). *Result:* cured. No evidences of tuberculosis elsewhere; good family history.

100 (see 63). P. The patient was a pale, weak, anemic dressmaker. Three months previously she suddenly developed a pain in the bladder and painful, frequent micturition, beginning rather gradually and getting worse. A few weeks later several slight attacks of hematuria. The *bladder* examination shows that the whole vault is converted into a red, irregular mass with pus in the interstices, while about the left ureteral orifice is an irregular tuberculous mass with pus in its centre; the vaginal portion of the *left ureter* is converted into a dense, hard cord. *Urine:* from *bladder*, acid, considerable albumin, many pus, red blood and epithelial cells, *sterile* on usual media, *Tubercle bacilli* in small number; from *left kidney*, acid, considerable albumin, many pus and red blood-cells, *sterile* on usual media, *Tubercle bacilli*; from *right kidney*, acid, no albumin, no pus or red blood-cells, *sterile*, no *Tubercle bacilli*.

CASES OF INFECTION WITH STRONGYLOIDES INTESTINALIS (FIRST REPORTED OCCURRENCE IN NORTH AMERICA).

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(Plates II and III.

During my term as assistant resident physician in the Johns Hopkins Hospital, in the service of Professor William S. Halsted, the following case came under my care:[1]

J. B., aged 52 years, born in Germany, was admitted to the hospital December 10, 1896, complaining of pain and of a tumor in his right side. The family history was good.

Past History.—The patient had measles as a child. There is no history of typhoid fever, rheumatism or pneumonia. He was always well and strong as a boy; his appetite and digestion were good. He does not smoke at all, and drinks very moderately; he denies venereal disease.

Until 8 years ago the patient lived in Bavaria, in the small town of Passau. Here he worked as a tailor and never travelled away except once or twice to Wiesdorf, which is only a few miles from Passau. Eight years ago he started from the latter place and went directly to Hamburg, sailing thence by steamer to New York. From New York he came to Brooklyn, Maryland. Here he lived for two years, farming. He then moved to 140 Chapel Street, Baltimore, where he has been ever since working as a tailor. He states that on the voyage over the ocean there were a number of Italians on board, but he did not associate with them. He has had fair health up to about four years ago, when he began to suffer from diarrhea. At first he had only one or two move-

[1] The report of this first case was ready for publication in June, 1898. At that time, owing to the breaking-out of the Spanish-American War, I was separated from my notes, which have only lately been restored to me.

ments a day. For the past three years he has had from two to five stools daily, and lately they have often been associated with a certain amount of blood. He has had at times burning sensations in his intestines when not at stool. There is no history of diarrhea among his associates.

Present Illness.—In October, 1896, the patient fell asleep on the ground one evening and did not awaken until night, when he felt very cold. He went home and the next morning felt perfectly well. Three weeks ago he first noticed pain and some swelling in his right side under the lower border of the ribs. He attributes this trouble to the exposure on the night in October above-mentioned. The swelling has gradually increased in size. He thinks it has grown more rapidly in the past week. He states that he has had no chills or fever and no sweats. He has had a slight cough for the past two weeks which, he thinks, has grown a little worse lately. He has had no expectoration.

Physical Examination.—The patient looks sick. The skin is somewhat sallow, the complexion muddy; the malar bones of the face are prominent; the conjunctivæ and finger-tips pale. The tongue is covered in the center with a light yellow coating. The body is emaciated; the muscles and fascia over the thorax are sparely nourished. Both sides of the chest move equally. Vocal fremitus seems normal. On percussion, the note is somewhat hyper-resonant over both sides in front of the axilla and over the back. There is no abnormal dullness. On auscultation, the respiratory sounds seem normal though perhaps slightly enfeebled over the right base. The pulse is 94, regular. The tension is slightly increased.

Heart.—The area of cardiac dullness is not increased beyond normal limits. The point of maximum impulse is in the fifth interspace in and inside the nipple line. At the apex the first sound is slightly prolonged, but there is no distinct murmur. At the base both sounds are clear and of normal relative intensity. The abdomen is rather full and, on percussion, somewhat tympanitic except over the right side, where there is dullness in the region of a tumor varying slightly with the movements of the patient. On the right side over the cartilages of the 10th and 11th ribs is an oval swelling, smooth and distinctly fluctuating. It is not particularly painful on pressure and the skin over it is not

reddened. It measures 7½ cm. in its greatest diameter. Between this swelling and the spinal column is a second tumor, about 1 cm. in diameter, extending almost from the mid-axillary line to the spinous processes, and from the 12th rib, over the crest and posterior surface of the ileum, for a distance of 7 cm. It is soft and fluctuating, and apparently goes downward into the iliac fossa. The skin over this second tumor is adherent, reddened and thickened in the central portions. There is no swelling or crepitus at the hip-joint. There is no curvature of the spinal column. No tenderness is elicited on pressure along the spine.

Liver.—Flatness begins at the lower border of the 5th rib. The lower border of the dullness cannot be clearly made out; it merges into abdominal tympany at the costal margin. The edge of the liver cannot be felt.

The *spleen* is not palpable.

On December 12, under cocaine anesthesia, Dr. Young made an incision 8 cm. long following the direction of the crest of the ilium over the posterior swelling. The subcutaneous tissues were edematous and contained here and there small pockets of pus. At a depth of 2 cm. an abscess cavity was reached and a large amount of thick pus containing a few shreds of tissue was evacuated. The pus was of a brownish-red color and anchovy-like in appearance. On inserting a probe a large cavity extending upward and inward for 10 or 12 cm. could be made out.

The anterior tumor was then incised and found to be connected with a cavity in the liver, which was about 5 or 6 cm. deep by 2 or 4 cm. wide. A probe could be passed through the wound in front and out of the posterior incision. The entire abscess cavity contained about 800 cc. of pus.

Microscopic examination of the pus showed a few necrotic liver cells, numerous actively motile specimens of *Amœba dysenteriæ*, and a number of large granular cells. Cultures from the contents of the liver abscess all proved sterile.

On the day following the operation the temperature rose to 102° F., the pulse being 136. The patient had several soft, almost fluid, reddish-brown stools. Microscopic examination of the stools showed, in addition to many epithelial cells, leucocytes and red blood-corpuscles, numerous slightly motile specimens of *Amœba dysenteriæ*, a fair number of *Trichomonas intestinalis* and the

embryos of a nematode, which were later identified as the rhabditis forms of *Strongyloides intestinalis.*

The examination of the blood showed slight oligochromemia. There was no marked poikilocytosis. No malarial or other parasites were present. On the following day the blood was again examined for malarial or other parasites, but the result was negative. The blood count showed 3,412,000 red corpuscles and 32,100 white corpuscles to the cubic millimeter. The hemoglobin registered 48 per cent. A differential count of the white corpuscles showed:

Polymorphonuclear leucocytes	88.3	per cent
Small mononuclear leucocytes	7.5	"
Large mononuclear leucocytes	2.4	"
Transitional forms	1.0	"
Eosinophiles	.3	"

The stools were examined daily until the death of the patient, which occurred 10 days later. Their number varied from 3 to 6 every 24 hours. They were always very thin and almost fluid, of a reddish-brown color and occasionally contained flakes of mucus. The odor was very foul. Microscopic examination invariably showed, in addition to fecal material, the three parasites, *Amœba dysenteriæ*, *Trichomonas intestinalis*, and embryonic *Strongyloides intestinalis*, besides red blood-corpuscles, leucocytes and many epithelial cells.

At first only one or two *Strongyloides* embryos were present in a single drop of feces, but later the number increased and toward the end 6 or 8 were often found in one drop.

The number of epithelial cells in the stools was often very great, the nematodes being frequently encountered lying in masses of epithelium. Amœbæ were found daily in the discharge from the liver abscess. *Trichomonas intestinalis*, and particularly the nematodes, were carefully sought for many times, but were never found in it. The temperature from the time of the operation until death varied between 101° and 102° F. The blood was again examined for parasites on December 18 and on December 22, but the result was found negative on both occasions. On the latter date the blood count gave: red cells, 3,244,000; leucocytes, 36,000; hemoglobin, 44 per cent. A differential count showed:

Polymorphonuclears	90.0 per cent
Small mononuclears	7.2 "
Large mononuclears	1.6 "
Transitional	.9 "
Eosinophiles	.1 "

The urine generally showed a slightly acid reaction. There was a small amount of albumin present but no sugar. Microscopically, a few epithelial cells of the pavement and high cylindrical variety and a fair number of hyaline and granular casts were observed. No parasites were found. On December 25 the following clinical note was made: The patient is much emaciated and seems very weak. The conjunctivæ and finger-tips are very pale. He has had five fluid stools to-day, all containing some blood. The last was discharged involuntarily into the bed-clothes. The blood examination was again negative for parasites. The blood-count showed: red cells, 3,180,000; leucocytes, 30,000.

The patient gradually grew weaker and the pulse became feeble and running; he sank and died on the following day, December 26.

Necropsy by Dr. Livingood 2 hours after death.

Anatomic Diagnosis.—Amœbic dysentery; ulceration of the large intestine. Abscess of the liver. Retroperitoneal abscess. Operation wounds. Intestinal infection with *Strongyloides intestinalis.* Parenchymatous degeneration of the kidneys. Fatty degeneration of the liver. Parenchymatous degeneration of the heart-muscle; atheroma of the aorta.

Exterior.—Body of a sparely built man, 163 cm. long; markedly emaciated; the abdomen is scaphoid-like; the body still warm; rigor mortis is marked; there is slight livor mortis over the back. No edema and no general glandular enlargement are present; several tophi may be seen on the edge of the concha of the right ear. There is no joint involvement and no scar on the penis. Over the sacrum and knees are superficial abrasions. The subcutaneous fat is scanty.

In the right flank below the tenth rib in the mid-axillary line above the highest point of the crest of the ilium is a shallow sinus due to the operation incision and measuring 3 by 4 cm. The edges of this opening are congested and beneath them the tissues are infiltrated with foul-smelling, bloody pus. This sinus com-

municates by a broad fistula with a larger incised opening in the back. This latter incision reaches from the middle of the back to the posterior axillary line, beginning about the second dorsal spine and extending downward and forward for a distance of 10 cm. The edges of this opening are injected and swollen, and beneath them there is infiltration with the same faint yellow, foul-smelling pus. The floor of the incision is formed by the erector spinæ and ilio-lumbar muscle. A probe can be passed upwards and forwards through the first opening and downward into the pelvis.

Thorax.—The anterior mediastinum shows no irregularity; the right pleural cavity is slightly obliterated by fibrous adhesions between the upper right lobe and the thorax.

The pericardial cavity contains a small amount of clear straw-colored fluid. The parietal layers of the pericardium are smooth; the visceral layer shows several small white patches of fibrous thickening.

Heart.—The heart is small and weighs 250 grams; the heart-muscle is firm but pale in color. The valves are all normal and show no thickening. The endocardium is smooth. The aorta just above the valve shows patches of atheroma.

Lungs.—The left lung is moderately pigmented, partially collapsed and contains but little air. There are a few blebs of emphysema along the anterior border; the right lung is adherent by its upper lobe to the thorax as described above; its diaphragmatic surface is free; it is somewhat collapsed. On cut section the lungs appear normal; there is no bronchitis and no atheroma of the pulmonary vessels.

The *spleen* weighs 150 grams; it is not adherent; its consistency is firm; the surface is bluish-gray in color; the capsule is slightly wrinkled. On section its color is red-brown; the substance is rather soft. The trabeculæ and the Malpighian bodies are both visible.

Kidneys.—They are somewhat small and rather soft in consistency. The right kidney weighs 150 grams. Both present the same peculiarities. The capsules strip off readily, showing pale surfaces; the corticles are broad, measuring 8 mm. The striæ are not prominent. The pyramids are rather small and not deeply congested. The pelves and ureters are normal.

The *liver* weighs 1200 grams. The left lobe and the upper anterior portion of the right lobe are free from adhesions. The capsule over these portions is not thickened. There are rather firm adhesions between liver capsule and the posterior part of the diaphragm and between the walls of the liver abscess cavity and the anterior abscess wall. The lower anterior margin of the right lobe is slightly thickened and is the seat of an abscess cavity which communicates directly with the sinuses spoken of before. This abscess measures 5 by 7 cm. on the surface of the liver and extends about 4 cm. into the liver substance. The structures about it are infiltrated. The wall of the cavity is coated with greenish-yellow shreds. The cavity contains brownish purulent material of foul odor. The rest of the liver is of a yellow-red color and has a distinctly granular appearance. The lobules of the liver are distinct. On cut section the tissues are dry and fatty. The portal structures appear normal. The gall-bladder contains thick dark bile.

The peritoneal cavity contains no fluid. The parietal layer of the peritoneum is smooth and slightly opaque. The omentum is bound to the right side of the peritoneal cavity by rather firm fibrous adhesions; it is very adherent to the transverse colon, being wrapped about it. The descending colon is adherent to the parietal peritoneum by firm adhesions. Its superficial vessels are somewhat injected. The cecum and ascending colon are firmly adherent by thickened tissue to the parietal peritoneum. The appendix is slightly dilated at its distal end but is otherwise normal. On removing the transverse colon from the abdominal cavity several ulcers which had almost perforated and which had been covered by the adherent omentum were opened up. The intestine about these points was much congested.

On opening the large intestine the rectum and colon are seen to be the seat of widespread ulceration. The ulcers are, for the most part, shallow in the rectum, having an eroded, thickened, hemorrhagic appearance. They vary in size; the largest is irregular in shape, measuring 3 cm. long by 2 cm. wide. Many other ulcers of moderate size have shallow, smooth bases which are generally formed by the submucosa or by the muscular coat of the intestine. Their outlines are irregular, the edges slightly elevated, hemorrhagic and undermined. There are a large number of smaller, shallow ulcers with red margins and filled with a tenacious,

yellow material. As they grow larger they become more like the larger ulcers described above. About the middle of the transverse colon are two ulcers which have almost perforated. The small intestine is free from ulceration. There is a distinct catarrh of the duodenum and jejunum (particularly in the upper portion of the latter) with here and there an ecchymotic patch. The mucosa here is bathed in mucus, which in places is very abundant.

The abscess in the liver is connected with a large retroperitoneal abscess communicating with the skin openings first described. The wall of the abscess is formed by the thickened wall of the cecum and ascending colon above. In the lower part it has burrowed into the iliacus muscle. There is no direct communication between the cecum and the abscess cavity. The cavity contains, for the most part, foul-smelling, yellow pus. In the lower parts of the abscess the pus is creamy white. The abscess may be followed into the substance of the psoas muscle for a distance of 4 cm., penetrating almost to the vertebræ and deep muscles of the back. The vertebral column is intact. The aorta shows patches of rather diffuse atheroma.

The bladder is small and contracted. The membranes appear pale. The pancreas and other organs appear normal.

Microscopic Examination.—Motile *Amœba dysenteriæ* were found in scrapings from the walls of the liver abscess cavity and in the mucus from the ulcers in the large intestine. Many of the amœbæ contained red blood-corpuscles. The embryonic forms of *Strongyloides intestinalis* were found throughout the large and small intestines. The adult females (parasitic forms) were found in the duodenum and jejunum but not in the stomach, the bile-ducts, or pancreatic ducts.

Bacteriology.—Plate cultures from the heart's blood, peritoneal cavity, and bile were negative for organisms. From the liver a bacillus was obtained both in coverslips and in cultures; it grew on all the same media and appeared to be identical with *Bacillus coli communis.* From the psoas abscess *Bacillus proteus vulgaris* was obtained in coverslips and in cultures. Frozen sections from the heart, liver, and kidneys all showed parenchymatous changes in these organs.

Inoculation of rabbits, by the stomach or rectum, with portions of the stools containing embryos of *Strongyloides* was always unsuccessful.

As was stated, the three parasites were constant in the stools during life. *Amœba dysenteriæ* and *Trichomonas intestinalis* are such common and such well-known parasites that we will not stop to describe them here. *Strongyloides intestinalis*, so far as we have been able to ascertain from literature, has never been encountered before in North America. A detailed description of this parasite therefore seems desirable.

DESCRIPTION OF THE PARASITE.

The nematodes found in the stools measured from .30 to .60 mm. long by 16 to 22 μ wide. In fresh stools they were always very active, swimming both forward and backward with eel-like motions, quickly coiling themselves up or again straightening themselves out. They were often found intimately mixed with fecal material which sometimes seemed to closely adhere to them. They resemble the *Uncinaria* larvæ, except that they have a larger body. Many of these larvæ when placed in the stools in the incubator seemed to begin to molt after 20 hours and to slip out of their coverings or skins. Often some forms were observed half out, while others were just slipping out and casting off this enveloping membrane. After the nematode has gotten rid of this outer covering its structure can be made out more clearly. The cephalic extremity is then seen to be rounded and pierced by the buccal orifice, about which may be seen (but only in the larger forms) three or four papillæ. Next to the mouth comes a vestibule (buccal cavity) which undergoes a slight, gradual enlargement and then becomes slightly contracted. This is followed by the anterior portion of the esophagus, and then by a narrower, second portion of the esophagus. Next to this latter constricted portion comes the esophageal bulb, which encloses an apparatus for trituration composed of three chitinous teeth placed in this form $\hat{\gamma}$. Continuous with the esophagus is the intestine which ends in a teat situated on the right side of the animal just above the base of the tail. At times it protrudes slightly and particles can be seen to pass from it. Situated on the right side, about one-third of the distance from the bulbous portion to the tip of the tail, may be seen a whitish (roughly), oval-shaped area which represents the sexual primordium (Anlage). The tail is tapering and pointed. On each side of the body in the older forms, but not in the young embryos, may be

seen, beginning at the bulb of the esophagus, two longitudinal series of muscular plates placed very closely together. They can be distinguished from one another only by their nuclei. All the larvæ in the stools either died off in three or four days before attaining sexual maturity, or underwent another change to be described below. In only one or two forms could the sexual organs be distinguished. One of these forms measured about .6 mm. in length. The esophagus presented the same appearance as in the smaller nematodes, except that it appeared relatively shorter. The bulbous portion of the esophagus was large and the chitinous teeth were better marked. The four papillæ could be seen more distinctly. The tail was short, tapering quickly, and partially curled. The copulatory organ could be seen in the form of two very small spicules about the cloaca. These spicules were slightly curved and cone-shaped. This specimen when found was dead. No adult females were found; apparently the culture media or the temperature proved unfavorable for the full development of the free form of this parasite, for in a few days, as has been stated, the embryos died or else began to change their form. Those which underwent a change seemed to have, at first, much longer and more tapering tails, often rolled in a spiral manner. The parasites, therefore, looked thinner; they soon began to resemble young *Filaria*; they lost their rhabditis form and passed to the strongyloid form. The esophagus lost its chitinous teeth as well as its bulb and first segment, and became a cylinder which traversed the whole anterior half of the worm and then became continuous with the intestine. These forms grew no larger, but gradually their tails began to shorten. In a few days more they also died out in the cultures.

No eggs were found in the stools nor were the adult female strongyloid forms (mothers of the rhabditis embryos) ever seen on fecal examination. At the autopsy, however, throughout the duodenum and in the jejunum (particularly in the upper portion of the latter) adult female strongyloid forms, together with large numbers of the eggs, were found. The rhabditis embryos were observed throughout the small and large intestine and one or two dead specimens were seen about the pylorus of the stomach, though these might have only accidentally wandered there after the death of the host. The adult female (strongyloid form) has the aspect of a filaria or of a strongyle. It represents the strongyloid form

of the dimorphous species of *Strongyloides intestinalis*. These forms measured about 2.10 or 2.20 mm. in length by 32 to 39 μ in width. The body increases slightly and gradually in size from the head until about the posterior fourth of the body. It terminates behind rather suddenly in a short tail, the tip of which is rounded and slightly dilated. The surface presents a very fine, regular striation. The mouth is simple and possesses no armature. Beyond the mouth comes the esophagus which is nearly cylindrical; it takes up nearly a quarter of the length of the parasite and presents no enlargements or swellings. Next to the esophagus comes the intestine which could be easily confounded with it but for the difference in its color. The intestine ends at the base of the tail in an anus which has the appearance of a transverse slit. The vulva appears at the posterior third of the body on the side; there is a slight protrusion and a transverse slit; the uterus, which opens here, in the adult always encloses 5 or 6 eggs of a yellowish, granular appearance, ellipsoid and measuring 59 by 34 μ. The eggs are often seen in segmentation. It is still a question whether these parasites are parthenogenetic or whether they are true hermaphrodites. Grassi and Calandruccio view the reproduction as parthenogenetic, but Leuckart (27) believes that the worms are hermaphrodites. He bases his argument on the fact that in *Angiostoma nigrovenosum*, the female stage is preceded by one in which the genital canal produces spermatozoa. The eggs are oval and resemble those of *Uncinaria*, but they are usually a little larger, measuring from 60 to 70 μ by 34 to 39 μ. They were often joined together in strings of two or three. All stages of segmentation were observed. In some of them the embryos could be seen issuing from the shell.

HISTOLOGICAL STUDY OF THE TISSUES.

Liver.—Sections through the wall of the liver abscess show a necrotic granular matter, surrounded by a zone in which the cells stain poorly and are granular. In the walls of the abscess there is no marked increase in the polymorphonuclear leucocytes, though there are numbers of small round cells in the outer zone; still farther outside is a zone of connective tissue, which contains spindle cells and areas of small-cell infiltration. In this region, which is very vascular, numerous branching bile-ducts may be seen.

In the outer part of this zone many degenerating, swollen, fatty liver cells are found and small hemorrhages about the capillaries have occurred. In the edge of the necrotic zone, numerous pale bodies, resembling amœbæ, are present. They are more scanty as one goes farther outside. About the central veins of the lobules, often at some distance from the abscess wall, are areas of general necrosis of the cells. No bodies resembling amœbæ can be made out in these regions.

Kidneys.—Sections of the kidneys show parenchymatous degeneration. The epithelial cells of the convoluted tubules are somewhat swollen and granular. There is some albumin in the lumen of the tubules. In the glomerular spaces there is a small amount of albumin and a few degenerated cells. The straight tubules contain a few granular casts.

Spleen.—The spleen shows no pathological changes beyond a slight increase in the round cells of the Malpighian bodies. No engorgement is present.

Heart.—The heart-muscle shows simple granular degeneration of the muscle-cells. No evidences of fragmentation or segmentation of muscle-fibers are visible.

Large Intestine.—Sections of the large intestine near the ulcerations show the submucosa to be much swollen. The tissues appear edematous. The blood-vessels and lymph-channels are engorged. The fixed cells with their nuclei are swollen and many show fatty degeneration. The round-celled infiltration is marked throughout the edematous tissues, the cells being chiefly small round mononuclear cells. The number of polymorphonuclear cells is apparently not large. In the overlying mucous membrane the change is sometimes not so well marked. There are often superficial losses of cells. Many of the cells are distended with mucus and in places proliferation of the epithelial forms may be observed. The ulcers themselves present a necrotic zone. The cells here have lost their nuclei and power of staining and have a granular appearance. The intercellular substance appears also as a granular mass. Around the margins may be seen collections of polymorphonuclear leucocytes. The mucosa is no longer seen. Some of the sections show the ulcerations extending to the muscular coat, with the superficial muscle-fibers swollen and widened. The muscle is infiltrated with small round cells. Palely staining bodies (amœbæ) are found all

through the ulcers, particularly in the submucosa, and extending in the walls of the ulcers to the muscular coat. Sometimes they have penetrated into the muscular coat, where they lie along the intermuscular septum of connective tissue. A few bacilli and cocci may be seen scattered through the necrotic areas, particularly in the more superficial layers.

Small Intestine.—The sections of the small intestine, cut from the duodenum and upper portion of the jejunum, show in general a catarrhal inflammation with desquamation and in many places atrophy of the epithelial cells. The solitary follicles are often slightly swollen and there are infiltrations of small round cells about the glands. There is no increase of the eosinophiles in the tissues which contain the parasites or ova. In sections stained with Unna's alkaline methylene-blue only an occasional plasma cell can be seen.

The sections show in addition:

(1) Many eggs in various stages of segmentation, some containing embryos, generally lying in the bottom of the crypts of Lieberkühn. In these crypts the epithelium is much compressed and often atrophied. The nucleus lies at the base of the cell and about it no cell substance can, as a rule, be made out. Some crypts contain two eggs, and in such cases the epithelial cells seem markedly compressed and atrophied. About the crypts which contain eggs (particularly when they are segmenting or contain embryos not yet hatched), there are a few small round cells. The diameter of the crypts containing eggs or parasites is always considerably larger than that of the surrounding ones which contain none. In several sections, when the egg has burst and the embryo has escaped, the epithelium of one side of the crypt has disappeared. About these crypts there is some degree of proliferation, as is indicated by the karyokinetic figures seen in the nuclei of the surrounding cells. The epithelium of the rest of the crypt is very much compressed. Only the nuclei can be made out and scarcely any cell substance is visible. The underlying solitary follicles are somewhat swollen and there are infiltrations of small round cells about the crypt. In other crypts the egg rests on the basement membrane of the gland, the epithelium having entirely disappeared or being much compressed. Not infrequently bodies which appear (in transverse sections) to be small cysts are seen lying in the walls of the crypt, resting on

the basement membrane. Apparently the eggs have disappeared from these "cysts" leaving clear areas. There is no apparent infiltration with small round cells about these so-called cysts (Fig. 7).

(2) Pieces of the adult female cut longitudinally and transversely. Not infrequently portions of the female containing the vulva may be seen just penetrating into the lumen of the crypt, while others are lying longitudinally or cut transversely in the crypt. In some cases where the pieces of the parasite rest at the bottom of the crypt, with only one layer of cells between, there is slight infiltration with small round cells of the muscularis mucosæ between it and the blind ends of the glands, but no collections of polymorphonuclear leucocytes or evidences of cell death in the muscularis mucosæ were noted. The solitary follicles in the neighborhood are slightly swollen. In the sections which show the adult female cut transversely in the crypt there is sometimes an infiltration of small round cells about the crypt and at its base. A few karyokinetic figures may be seen in these sections and round, oval and spindle-shaped cells in the adjacent tissues. One section shows the adult female in the crypt, the epithelium being almost completely gone. There is considerable infiltration about the crypt, and a moderate number of polymorphonuclear leucocytes. Occasionally in sections which contain the adult parasite lying near the surface of the mucosa, the desquamation of cells is marked and many of the nuclei of the neighboring cells stain poorly (Fig. 6).

(3) Many of the crypts contain embryos. In these crypts there is generally a flattening and atrophy of the epithelial cells, the embryos appearing to compress the epithelium. In some places the cells are entirely absent from the crypt and at first sight it might appear that the embryos lay in the lymph spaces. Sometimes outside the crypt slight proliferation is indicated by the mitotic figures seen in the nuclei. In several of the sections embryos are apparently breaking out of the crypt, and have desquamating epithelial cells lying about them. One section shows an embryo beneath the epithelium of the villus; this finding may explain the way in which the parasite destroys and causes desquamation of the superficial epithelium. The parasite by its violent, rapid movements might easily have knocked off the overlying epithelium (see Fig. 5). The sections in the neighborhood of the embryos show no marked inflammatory changes, but infiltrations

of small round cells are not uncommon and the solitary follicles in the vicinity are slightly swollen.

SYNONYMY.

Anguillula stercoralis Bavay, 1877.
Anguillula intestinalis Bavay, 1877.
Leptodera stercoralis (Bavay) Cobbold, 1879.
Leptodera intestinalis (Bavay) Cobbold, 1879.
Pseudorhabditis stercoralis (Bavay) Perroncito, 1881.
Rhabditis stercoralis (Bavay).
Rhabditis intestinalis (Bavay).
Rhabdonema strongyloides Leuckart, 1883.
Strongyloides intestinalis (Bavay) Grassi, 1883.
Rhabditis strongyloides (Leuckart) Grassi.
Rhabdonema intestinalis (Bavay) R. Blanchard, 1885.

HISTORICAL REVIEW.

Normand, in 1876 (2), working in the Saint Mandrien Hospital in Toulon, in the microscopic examination of the feces of soldiers who had come back from Cochin China, discovered a nematode. Bavay (3), who, at Normand's suggestion, undertook a careful study of these cases, in a short description of this nematode, named it *Anguillula stercoralis*. A short time after (1877), at a necropsy of a man who had died from Cochin China diarrhea, Normand (4) found a second nematode, different from the first, and which occurred with the other in the intestine. In 1877, Bavay (5 and 6), to whom Normand had sent a specimen of the second parasite, found it in four other necropsies and also considered it as distinct from *Anguillula intestinalis*. In 1877, Zürn (7) noted that there occurred in Cochin China fowls a diarrhea attributed to an infection with *Anguillula stercoralis*, which had become developed in the walls of their intestines. This diarrhea, he stated, was very analogous to that attacking man and called Cochin China diarrhea. The death of the fowls resulted either from rapid debility or slowly from marasmus and anemia. This work was followed, in 1877, by the articles of R. A. Roux (8) and Laveran (9), who discussed the rôle played by *Anguillula stercoralis* in the Cochin China diarrhea and concluded that it was probably the cause of the disease. Libermann (10 and 11), however, declared

that the parasite was not the cause, but only an accompanying factor in Cochin China diarrhea. Dounon (12) in the same year made the first histological studies of the tissues in those dead from Cochin China diarrhea. He described small cysts within the crypts of Lieberkühn in the duodenum, which, from his pictures, were evidently the ova of the *Strongyloides intestinalis*. He also described inflammatory changes in the mucous membrane, and epithelial lesions which he attributed to the presence of the *Anguillula*. In 1878, Normand (13) described more fully the diarrhea of Cochin China. At first he found the parasite in all of the patients suffering with this malady and did not doubt that it was the exciting agent. The disease was especially prevalent among Europeans in Indo-China, but was not confined to the Cochin China colony. The epidemic extended from Singapore to Shanghai, all over Indo-China, and to some parts of the Malay Archipelago. Normand thought that sometimes the parasite might for a while prove harmless until a fever, an attack of indigestion, or some other cause bringing about a lessened resistance in the host, gave the parasite the upper hand. Normand restricted himself to drinking water brought from Europe, but despite this precaution had an attack of this diarrhea. He therefore concluded that the parasite might be introduced in other ways, and that, as Chinese gardeners fertilize their gardens with human excrement, the infection might occasionally occur through eating salads or vegetables. Chastang in 1878 (14) made observations in Saigon, Cochin China, on 22 cases of chronic diarrhea; he concluded that the *chronic* diarrhea of Cochin China is not of parasitic origin, because he scarcely ever found the parasite during the period of invasion of the disease. As a therapeutic agent he suggested chlorodyne. In the same year, Chauvin (15) demonstrated the same parasite in the stools of two soldiers returning with a severe diarrhea from Martinique. In 8 other cases from the same place the examinations of the stools were negative. He also found this parasite twice in 8 sick returning from Cochin China. Again, in the same year (1878), B. Grassi (16) suggested that in several animals anguillulæ were sometimes found which resembled those found in man. He met with these in rabbits, pigs, and squirrels. He considered them to be very like those of man and as evidently belonging to the same genus. They were, however, smaller, measuring 370μ long

and 5 μ in their greatest breadth. The esophagus measured 68 μ. The parasite inhabited the same region of the intestine as the human *Anguillula*. Grassi was never able to find a male specimen, nor could spermatozoa be demonstrated in these nematodes. He also found, in the feces of rabbits, embryos in which the esophagus showed the second swelling as in the parasites affecting man. In the stale feces in the rabbit-hutch, which was very dirty, he also found eggs and embryos like those of *Anguillula intestinalis* and also species of *Leptodera* and *Pelodera*; precisely those which Ercolani considered to be intestinal nematodes in a state of free life from dimorphobiosis. From a study of the work of Ercolani (17), who had already suggested dimorphobiosis for other parasites —among them *Ascaris maculosa* of the pigeon—Grassi, in view of the fact that he himself had discovered in the fresh feces of rabbits, eggs and embryos like those of *Anguillula* and upon cultivating these feces had found in a few days large numbers of male and female species of *Leptodera*, thought it not impossible that *Anguillula intestinalis* of the rabbit might be dimorphobiotic; but inasmuch as in the feces of rabbits not containing *Anguillula*, especially when the feces were damp and old, he found many *Leptodera*, he states, that before accepting this theory it is necessary to exclude from the cultures those nematodes which live free and which are simply contaminations. He also thinks that for this very reason Ercolani's work cannot be regarded as conclusive. He was not able to convince himself that *Anguillula intestinalis* lives free in a perfect state. In the stale feces of a man he found nematodes of rapid movements and like the embryos of *Anguillula intestinalis*. Later the caudal appendage became much longer than in *Anguillula intestinalis*. From this fact he supposed that these filariform larvæ were evidently coming directly from rhabditis larvæ of *Anguillula intestinalis*.

In 1879, B. Grassi and C. Parona (18) contended that *Anguillula intestinalis* was not confined to the region of Cochin China. In the feces from a patient living in Pavia, Italy, they found young forms which they thought were possibly the embryos of *Anguillula intestinalis*. In the same year these observers (19) found the embryonic forms in the stools of 21 patients. In one case which came to necropsy they found the adult *Anguillula intestinalis*. They were unable to obtain adult *stercoralis* forms

from these embryonic stages which they found in the stools. They thought that in all probability the parasite is not the cause of the Cochin China diarrhea, but that when present in large numbers it cannot be entirely innocuous to human beings. In the one fatal case, they found at necropsy atrophy of the gastroenteric canal with chronic gastroenteritis, atrophy and fatty degeneration of the liver, atrophy of the spleen and of the pancreas. Grassi in 1879 (21), in another more extensive article, reviews his work on the parasite. He points out that Parona and himself had proved that the parasite was not peculiar to the region of Cochin China, but also occurred in Italy, as was shown by the case observed by them in Pavia. In Milan also he had found *Anguillula* 30 times in 250 necropsies and 12 times in 100 examinations of the feces. He points out that the embryos are found in the feces, but that this does not hold good for the ova. In a man who had embryos in his stools during life, Grassi found *Anguillula* at necropsy. From his comparative studies on *Strongylus filicollis* he decided that the so-called *Anguillula stercoralis* is nearly related to the genus *Strongylus*, and should, therefore, be called *Strongyloides*. He reserves his opinion in regard to the harm the parasite does in man.

In 1879, J. Breton (22) also studied cases of persons suffering from diarrhea in Cochin China. He found the parasite in 10.9 per cent of cases of chronic dysentery and in 8.8 per cent of cases of chronic diarrhea. He never observed it during the acute period of the dysentery nor in the very bilious stools. In several cases of intestinal disorder he never found the parasite in any stage of the disease. Moreover, its presence, it appeared, was independent of the degree of the severity of the malady. (It is evident that he tried to put the various diarrheas and dysenteries of Cochin China into one class and to ascribe a single cause for all.)

In 1880, Perroncito (23), in a study of the parasitic diseases affecting the workmen of the St. Gotthard tunnel found, among other parasites, *Uncinaria* and *Anguillula intestinalis* in a large number of the cases. He studied the encystation of the young forms of these parasites and compared it to the encystation of *Trichina spiralis*, with the difference that the chrysalis can move with the animal. He claimed that the capsule contained a chitinous material and that the cyst was elaborated from the skin of the animal; that when they have cast off this skin they envelop

themselves in it for protection from drying and changes in temperature. In the same year Perroncito (24) stated that in all probability *Anguillula intestinalis* and *A. stercoralis* could have an action similar to that of *Uncinaria* in causing the miners' disease at the St. Gotthard. In the stools of many of these workmen he found ova. He believed that some of these belonged to *Uncinaria* and others to *Anguillula*, for on cultivating them, he thought he obtained two different parasites, one an embryonic *Rhabdonema*, and the other an embryonic *Uncinaria*. He concluded that *Anguillula* was a cause to some extent of the anemia prevailing among the workmen of the St. Gotthard.

In 1880, Luz (25) reported the finding of *Anguillula stercoralis* in the endemic diarrhea occurring in Brazil. He first encountered the parasite in an infant who had had diarrhea for a year.

In 1880, Bozzolo and Pagliani (26), in a study of the anemia of the workmen at the St. Gotthard tunnel, found *Anguillula intestinalis* and *stercoralis* in only one out of 11 cases, and, therefore, did not attribute to it an important rôle in this anemia. They were unwilling to state, as Perroncito had done, that *Anguillula stercoralis* and *intestinalis* have an action very like that of *Uncinaria*, but concluded that this point was still undecided. In all the fatal cases in which they had been able to demonstrate eggs in the feces during life, they found *Uncinaria* in the duodenum at necropsy.

In 1881, Perroncito (27, 28) studied the adult free stage of this parasite outside of the human body. He ascribed to the male a mean length of .7 mm. and a breadth of .035 mm., to the female a length of 1 and a breadth of .05 mm. He placed larvæ found in the feces in the incubator, and after 30 hours a number had already come to the adult stage; not a few of these had copulated and Perroncito observed the uterus of the female filled with eggs, sometimes partially segmented. He was fortunate enough to witness the copulation and describes it as follows: "The act has a short duration of from 40 to 50 seconds. The male rolls the tail about the body of the female about the level of the vulva; he introduces his spicules into the vulva and then rolls himself up rapidly 2 or 3 times around the female, pressing her with force. She makes an effort as if to disengage herself from the embrace of the male, but the ejaculation is not delayed long. The male relaxes its spicules

but leaves them still attached to the female for 2 or 3 seconds and then finally abandons her." After the copulation, the eggs begin to pass into the uterus. They accumulate sometimes in such abundance that the parasite becomes considerably distended with them and they compress the intestine. Perroncito believed that *Anguillula stercoralis* is a species quite distinct from *Anguillula intestinalis* and proposed the name *Pseudorhabditis stercoralis* for the former.

In 1882, Perroncito (29) confirmed the work of Grassi in regard to the *Anguillula* of the rabbit. He also found only female parasites in the intestine of the animal.

In 1882, B. Grassi (30) argued against Perroncito's views published in 1880. In several necropsies, in various climates, whenever he found ova in the feces during life (which he regarded as *Uncinaria* eggs, whereas Perroncito had thought that some were *Uncinaria* and others were *Anguillula* eggs) Grassi also found *Uncinaria* in the small intestine after death, the number of parasites being proportionate to the number of eggs. When no ova were demonstrable in the feces no *Uncinaria* were found at necropsy in the small intestine; but in the small intestine in some of these cases *Anguillula intestinalis* was found in abundance despite the total absence of eggs from the feces. He thinks the eggs described by Perroncito as occurring in the feces belonged to *Uncinaria.* In stools from patients in the hospital in Milan during the winter, Grassi frequently found the larvæ of *Anguillula intestinalis* and what Perroncito had looked upon as those of *Anguillula stercoralis.* In dead bodies in winter Grassi could never demonstrate *Ang. stercoralis,* but *Ang. intestinalis* embryos were observed commonly enough. Grassi insisted that the larvæ found in the intestine underwent the development previously described in his work with the Paronas, namely, they formed *Ang. intestinalis* directly. The larvæ were taken from a corpse that contained only *Ang. intestinalis.* He thought that either Perroncito had been deceived by free nematodes occurring as contaminations of his culture material, or that the larvæ must change somewhat when cultivated under certain conditions. Grassi states that, if Perroncito's observations are correct, he would be inclined to suppose that *Ang. intestinalis* is dimorphobiotic as *Ascaris nigrovenosa,* and that *Ang. stercoralis* represents the free form of *Ang. intes-*

tinalis. The absence of males in the intestine inclines him to compare it with *Ascaris nigrovenosa.* He does not regard it as a blood-sucking parasite, but thinks that it may often be innocuous.

In 1883, Leuckart (31) carefully described the *Ang. stercoralis* and its relation to *Ang. intestinalis.* He showed from cultivations that these two parasites represented two successive forms of one and the same species—that *Anguillula intestinalis* was the parasitic form and *Anguillula stercoralis* the free form. From the embryonic forms of *Ang. intestinalis* he obtained the adult *stercoralis* form and thus definitely settled the question of the dimorphobiosis of this parasite. He proposed the name of *Rhabdonema strongyloides* for the parasite. He regarded *Ang. intestinalis* as hermaphroditic, basing his argument on the fact that in *Angiostoma nigrovenosum* the female state is preceded by a stage in which the genital canal produces spermatozoa. In his description of the adult free form of this parasite he attributes to the male an average length of .7 mm. and a breadth of .04 mm.; to the female a length of 1.02 mm. and a breadth of .075 mm.

In 1883, Seifert (32, 33) concluded, from a case in Gerhardt's clinic, that the parasite is probably innocuous, though it may be present in large numbers. He states that he found male fern of no value in the treatment of the disease. He obtained from the embryos of *Anguillula intestinalis* in the feces, by cultivation, *Anguillula stercoralis.*

In 1883, I. Toth (34, 35) expressed the opinion that the parasite played a preponderant rôle in the production of the anemia among the workmen in Schemnitz, Hungary. He believed it to occur more frequently than *Anchylostoma* (= *Uncinaria*). In his hand, male fern proved satisfactory in the treatment of the condition, and he states that he cured 16 cases with it. Oerly, however, could never find anything besides *Uncinaria* in cases from Schemnitz; and Blanchard (48) also was satisfied that *Rhabdonema* did exist in these mines.

In 1883, B. Grassi (37) denied that male fern had any effect upon the parasite; moreover, he still insisted that *Ang. intestinalis* is harmless and that no disease can be ascribed to its influence. He referred to the article of Sahli, published in 1883 (38), who had tried male fern without effect, and made the broad statement that neither this observer or any one else had been able to expel a single

adult *Ang. intestinalis* by this anthelmintic. He quotes another case of chronic consumption where male fern was given and where the patient finally succumbed to the effects of the drug, although the feces up to the time of death contained the parasites. He states that the dimorphobiosis of *Anguillula intestinalis* is certain, that the embryos found in the stools may become the adult free form of the parasite, or they may directly become *Ang. intestinalis.*

Perroncito (39), in a communication published in 1883, maintained that male fern was of great efficacy in expelling the parasite; he reported 30 cases of cure and referred to the 16 other cases cured by Toth. It is sometimes necessary, he stated, to give the drug for 6 days, in doses of 2 to 4 grams per day, and that the cure was then certain. He still held that the parasite caused some of the anemias at the St. Gotthard and at Schemnitz. He did not regard it as dimorphobiotic, and insisted that he had not confused *Anguillula* eggs with *Uncinaria* eggs. With respect to the case reported by Grassi, of a young boy, with diarrhea and *Anguillula* embryos in his stools, he argued that the patient was not cured but that the symptoms were merely alleviated for a time.

In 1883, G. Strambio and C. Colombo (40) reviewed briefly the literature and referred to the controversy between Grassi and Perroncito in regard to this parasite, without expressing a definite opinion as to its pathogenic rôle.

In the same year, B. Grassi (41) published a paper in which he referred again to the case of the boy who had a return of the diarrhea and anemia and who had embryos of *Anguillula* in his stools, but who, after 2 months, was cured without anthelmintics, though his feces still contained the parasite. He insisted that this instance proves the harmlessness of the parasite and that Perroncito's citation of this case against him was not substantiated by facts.

In 1884, Golgi and Monti (42, 43), and also later (44), found, in the feces of a patient embryonic forms and in the intestines at necropsy *Ang. intestinalis* but no adult *stercoralis* forms. They thought that the latter was only a free form. They were not contented, however, with this assumption, but went further and cultivated the embryonic forms in the feces at a temperature of 20 to 22° C. After three days they obtained adult *Ang. stercoralis* forms. Many females were present, some containing from 20 to 30 eggs, often in segmentation with embryos inside; some embryos they

saw issuing from the eggs. They concluded that *Ang. stercoralis* was not a parasite, but that they had to deal with a worm which was dimorphobiotic and that *Ang. stercoralis* was the free stage. They found the parasite only once in the stomach. The study of sections showed that the eggs were never found except in the regions in which *Ang. intestinalis* was present. Inasmuch as microscopic study of tissues from their necropsies demonstrated a loss of the epithelium of the glands, proliferation of epithelium indicated by division of nuclei and karyokinesis, swelling of the solitary follicles and diffuse infiltration with leucocytes, they were inclined to believe that *Anguillula* was not an innocent parasite and to attribute a pathological importance to it. Nevertheless, since the presence of other lesions at their necropsies rendered it possible to explain those of the intestines in some other way, they concluded that the question of its pathological rôle was not settled. They never found eggs in the feces except after a drastic, when they found them mature, containing almost complete embryos. They tried male fern without any effect. Not a single *Ang. intestinalis* was ever expelled. The fact that the parasite is often hidden and sheltered in the glands might very well explain, they thought, the uselessness of male fern.

In 1884, Grassi and Calandruccio (45) expressed the opinion that, inasmuch as *Ang.* (*Rhabdonema*) *strongyloides* is found under only one form in the intestine, it is impossible to say definitely whether this parasite is hermaphroditic or parthenogenetic, although the earlier observations of one of them rather indicated that it was parthenogenetic. They stated that the adult female *Ang. strongyloides* of man lays eggs from which embryos are developed. These embryos are found in the feces, and have a different form from their mothers. Outside of the body they may undergo two changes: (1) They may assume another shape, becoming long and thin, acquiring a relatively long esophagus, and losing the esophageal teeth, that is, showing more and more the characteristics of *Ang. intestinalis*; or (2) they may become long and thick, cast their cuticle, and become mature males and females. This second generation, which was held by Perroncito to be a distinct species, Grassi and Calandruccio show to be merely the free form of the same parasite. These males and females copulate and produce young which never mature outside of the body. When

the cultures of the feces were kept at ordinary room temperature the development, as a rule, skipped the free living generation; but at a continued temperature of 37° C. the free generation was more often obtained. These two observers believed that either generation, the filariform or rhabditis, if introduced into man, will cause the disease.

In 1885, Grassi and Calandruccio (46), and Grassi (47) continued their work on this parasite; they verified the dimorphobiosis not only of *Ang. intestinalis* of man, but also of *Rhabdonema longum* of the sheep. The parasite of the sheep is larger than the corresponding one in man. From their work on this parasite they conclude that the *Anguillula* of man is parthenogenetic.

In the same year, Blanchard (48) gave a careful description of this nematode. In his opinion, it represented a helminth whose embryos develop in the free state into sexual rhabditis forms, and only the descendants of these should be considered as parasitic. According to Blanchard, therefore, the cycle of development presents a series of generations, alternately free and parasitic—a characteristic belonging more particularly to the family of Rhabdonemides. Blanchard believed that *Ang. stercoralis* should be erased from the list of parasites of man, since, in spite of its sexual maturity, this form only represents an intermediate state developing freely and making part of the cycle of evolution of *Anguillula intestinalis*. The latter only, in his opinion, should be regarded as a parasite of man.

In 1885, Lutz (49, 50) wrote of the occurrence of the *Rhabdonema* in pigs and confirmed his former statements in regard to the presence of the human *Ang. intestinalis* in cases of diarrhea in Brazil. The human diarrhea resembled that described and designated as Cochin China diarrhea. Lutz believed the nematode to be the cause of the disease in Brazil. He showed, further, that the species found in the pig is a distinct one and rare in Brazil, whereas the one found in man is very common there.

In 1886, Radetski (51) reported for the first time in Russia a case of diarrhea in a patient infected with *Ang. intestinalis*.

In 1886, Golgi and Monti (52), in a more complete report, described the lesions of the small intestine in cases in which this parasite was present. In one of these cases they found embryos in the common duct and in the pancreatic duct. The examination of

many sections of the small intestine showed the adult parasites, or pieces of them, with the part of the body containing the genital aperture bent and introduced into the lumina of the crypts of Lieberkühn. In the glands themselves they observed many larvæ in various portions, especially under the valvulæ coniventes. These observers do not attribute the death of their patients or all of the lesions found at autopsy to this parasite, but, on the other hand, they did not think it right to deny a morbid influence to this parasite inasmuch as they found an irritated state of the epithelium of the glands occupied by the nematodes, desquamation of the epithelium and alteration of the epithelium of the glands of Lieberkühn, and swelling of the solitary follicles with diffuse infiltration with leucocytes in the muscularis mucosæ between it and the blind ends of the glands. That the parasite causes destruction and regeneration of the epithelium was indicated by the numerous divided nuclei and karyokinetic figures that were seen, particularly about the glands which contained eggs. In their cases a catarrhal enteritis existed. They pointed out the difference in size between *Anguillula* eggs and *Uncinaria* eggs, the latter being smaller and having a thicker shell. They still insisted that male fern was of no value in the treatment of the disease.

In 1887, Grassi and Segre (53) confirmed the work of Grassi and Golgi and Monti in regard to the direct transformation of rhabditis filariform larvæ without passing through the adult free stage. In over 20 cultures they observed the direct transformation and obtained filariform larvæ. When they kept their cultures at higher temperatures they more often obtained *Ang. stercoralis*, whereas at lower temperatures more often filariform larvæ developed, although these results were not always constant. They suggest that the embryonic *Ang. intestinalis*, which is potentially a male (not certainly, however, for the rudimentary genital organs are not distinct), either dies or becomes a male *Ang. stercoralis*. Or else those which are potentially females become either females of *Ang. stercoralis* or filariform larvæ, because in numerous cultures containing many filariform larvæ and few *Ang. stercoralis* the latter always appeared as males, while, on the other hand, when there were many *Ang. stercoralis* they were almost always females (8 to 1). These observers conclude, therefore, that *Ang. stercoralis* is not necessary for the perpetuation of the species. In the same

year they also verified the dimorphobiosis of *Anguillula* of the sheep, though they state that it is not so marked in this latter parasite. They found that nearly all of the adults of the free generation were females, whereas in the *Rhabdonema longum* they never found larvæ from the free generation, and hence concluded that this form is doubtful or very rare.

In 1888, Mestayer (54) gave a resume of the treatment of Cochin China diarrhea without adding anything new to our knowledge of this parasite.

In 1889 and 1890, Calandruccio (55) found, for the second time, the parasite in Catania, Sicily, in a case of diarrhea. He showed that the parasite was dimorphobiotic, exhibiting two different generations.

In 1891, Sonsino (56) reported three cases of rhabdonemiasis. His first patient, a laborer, had had a severe, uncontrollable diarrhea for three months; he was much emaciated and at times had considerable vomiting. He was accustomed to work in the woods and often drank dirty water. The stools were of a yellowish-gray color. Microscopically they contained many leucocytes and embryos of *Anguillula*, but no eggs or full-grown parasites. In addition, Sonsino found two varieties of infusoria, the cercomonas and a variety resembling it. The patient was given four half-drachm doses of thymol, but no good effects resulted from its administration, except that some of the embryos were later found dead in the stools. This patient died shortly afterward. At necropsy nothing was found but atheroma of the aorta and the aortic valves. The intestines showed hyperemia with slight erosions of the small and large intestinal mucosa. In the duodenum were found characteristic embryos and eggs joined two and three together, and embryos were present throughout the intestinal tract. In the contents of the intestine no adult parasites could be demonstrated, but the necropsy was performed 23½ hours after death. The second patient was a hunter, who presented a marked anemia of the skin and mucous membranes. He had a few *Trichocephalus* eggs and numerous rhabditis embryos in his feces. The blood examination showed a normal proportion between white and red blood-corpuscles. The latter were paler than normal. The patient was treated with thymol and perchloride of iron. After some months he recovered and all the rhabditis embryos disappeared from his

stools. Sonsino's third patient had had diarrhea and stomach trouble for a year and also a catarrhal cough. The examination of the lungs and of the sputum was negative. An abscess developed in the right thigh. Examinations of the stools showed mucus, undigested food, and rhabditis embryos. Two drachms of thymol were given but with no good effects. The thymol was continued next day, but the patient could not stand the treatment and it was stopped. The man died shortly afterward. At necropsy there was only a slight bronchitis. No tubercle bacilli were found. The liver was pale and slightly fatty; the spleen enlarged and the pulp soft. The kidneys were normal. The author attributed the trouble to the infection with *Anguillula*. The intestine was distended with gas, except the upper part of the duodenum, which was slightly hyperemic. The duodenum contained a whitish-yellow material. The mucous membrane was slightly hyperemic. In the jejunum there was much mucus, and stripes of dark pigment occurred with slight hyperemia and small hemorrhages, particularly in the free portions of the valvulæ coniventes. In the ileum there was nothing of note. The large intestines showed superficial ulcerations. The adult female parasite was found in the duodenum and jejunum. Sonsino believed that the symptoms exhibited by these three patients were due to infection with this parasite. He concluded that the anemia and intestinal catarrh were caused by its presence, as in the Cochin China diarrhea. In one case the author could explain the death but not the symptoms. He thought that the damage done is proportionate to the number of parasites, and that a small number may be present without producing marked symptoms. He was not prepared to say how this condition is brought about, although it might probably be due to a poisoning from the metabolism of the parasite. Sections cut with the microtome showed eggs with embryos and embryos free in the rhabdonema state in the villi of the mucosa. He concluded that thymol may sometimes be of value in the treatment of the disease.

In 1892, Ilberg and Gerhardt (59) reported the case of a patient who had complained of gastric disturbances, loss of appetite and fever. Edema and anemia were present. This case reminded Gerhardt of one he had previously seen infected with *Anguillula*. Upon examination of feces, embryos of *Anguillula* and a few

Uncinaria eggs were found, and later a few *Trichocephalus* eggs. The blood showed the malarial plasmodium. Under these circumstances it was impossible to estimate the importance of the part played by *Anguillula* in producing the condition, but Gerhardt does not think that this parasite is as nocuous as the *Uncinaria*.

In 1895 and 1896, Silvestri (60, 61) reported the case of a patient with nervous symptoms which he believed to be due to this parasite. The man had acquired syphilis at 21 years of age, had undergone special treatment for it and was apparently cured. His later illness had begun with loss of appetite and gastric disturbances. These symptoms were followed by fits of vertigo. His general condition was such that he had been obliged to stop work. He had been treated for gastritis, anemia, syphilis, and epilepsy, respectively. During treatment with potassium bromide for the last disease he became much worse. When he came to Silvestri he showed considerable anemia and complained of dizziness, want of appetite, and general weakness. The physical examination was negative. The pulse was rather rapid; the urine normal in quantity and quality. Nothing being apparent but the anemia, the feces were examined, with the result that large numbers of the larvæ of *Anguillula intestinalis* were discovered. At first Silvestri did not attribute the condition of the patient to the presence of *Anguillula intestinalis*. Nevertheless male fern (8 grams) was given after a fast, and many dead *Anguillula* were passed. The treatment was continued the next day and apparently all the parasites were expelled. After this the patient began to improve. No more fits of dizziness occurred. His other disturbances ceased and the general weak asthenic state rapidly disappeared. In view of these facts Silvestri concluded that the condition had been due to the infection with the parasite.

In 1895, P. Teissier (62) reported a case of an emigrant from French Guiana, a gold-seeker who had returned to Paris in 1891. He had been sick in Guiana with fever, marked general anasarca, anemia, loss of appetite, and vomiting. On the voyage to Paris the anasarca disappeared but the fever persisted. On his entrance to the hospital his anemia was profound. Under treatment with quinine and Fowler's solution from September 21 to the latter part of November, he was cured and went to Brazil to search for gold a sec-

ond time. He was exposed to change of climate and bad weather, alcoholic excesses, etc. He again became very sick. His condition not improving, he returned to Paris and re-entered the hospital (three months after his arrival) on February 20, 1895. On entrance he was very feeble and anemic, had diarrhea and some fever. The urine showed no albumin and no sugar. The spleen was somewhat enlarged. There was slight bronchitis and a venous souffle in the vessels of the neck. For a few days following he had an irregular fever from 36.5 to 40° C., which, however, completely disappeared in 8 days under quinine. On February 23, the blood was examined for the first time for Laveran's organisms. No plasmodia were found, but a number of nematodes were present. During the next day and night the blood examination showed the same parasites. A short time after the disappearance of the fever the embryos disappeared from the circulating blood and the author was not able to find them in either of the successive day or night examinations. The author states: "From the first day we found the same embryos in the fecal material, together with the more fully developed worms and eggs in different stages of development." The examination of the urine was always negative. The patient remained in the hospital until March, expelling all the time with the stools a variable number of nematodes, living or dead. The spleen was still enlarged and the diarrhea moderate and intermittent. After a month's absence he returned with an area of bronchopneumonia. During the period of his stay in the hospital nematodes were never found in the blood. The parasites in the feces under mercurial treatment decreased in number. Soon after, his strength began to return and his diarrhea disappeared. The anemia alone persisted. He recovered and has since been well.

Teissier obtained the adult *stercoralis* form from the embryo rhabditis form found in the stools. In the feces he also found ova in different periods of segmentation and adult females measuring 1.29 mm. long. He injected blood-serum from his patient into the ear-vein of rabbits without result. The embryos found in the blood he describes as small cylindrical worms, transparent and almost homogeneous, comparable to the embryos of *Filaria* of the blood of man, except that they were a little longer and relatively a little thicker; one extremity was thread-like and terminated

in a point; the other was slightly swollen. With objective Veruck they presented no structure, apparently consisting of masses having a yellow-brown tint. With the highest magnification they were finely granular with the granules arranged in two rows about a central canal. The length was 240 to 220μ, the width 10 to 12μ. They were very motile, possessing violent movements. At first five or six would be seen in each slide, but they gradually diminished. Teissier found the adult stercoral forms, male and female, in fresh stools immediately after they were passed, and concluded that these forms must have existed in the intestine, so that the view that they develop in the fecal matter only outside of the intestine is incorrect. He was in some doubt whether he had found a new variety of *Filaria* or whether he should connect the parasite observed in the blood with the adult parasites found in the intestine. The classical description of *Filaria* so well suited his blood parasite that he believed the condition to be one of filariasis up to the time that he found the forms in the feces—an observation which showed him the error of his previous supposition. The disappearance of the parasites from the blood was, in Teissier's opinion, a strong argument against their being *Filaria*. He believed that *Ang. stercoralis* gives birth to small embryos which could easily gain access to the circulating blood through the breaks in the mucous membrane of the intestine; that the fever of the patient was due to the presence of helminths in the blood, whereas the diarrhea and anemia were caused by the intestinal parasites. The diarrhea ceased with the disappearance of the parasite from the stools. The blood examination of his patient showed: Red blood-corpuscles, 1,033,500. Slight poikilocytosis. The leucocytes were reduced in number, but were normal in appearance.

In the next year, 1896, P. Teissier (63) again stated that *Anguillula stercoralis* might be a parasite of man and that it can undergo its whole cycle of development in the intestine. He was unable to infect rabbits either by intravenous injection of the blood of his patient or by feeding fecal material containing nematodes. Moreover, by the injection of *Anguillula stercoralis* intravenously separated by dilution, he failed to infect rabbits. He therefore took up experiments with the frog. He chose this animal to see if the embryo *Anguillula stercoralis* could be proved to pass into the blood by observing under the microscope the inter-

digital membrane. In this respect he failed, but stated that he infected all the frogs but one, and that he produced in the animal all of the evolutionary forms of *Anguillula stercoralis*, "but with an *Anguillula* increased in all of its dimensions, in its volume, representing a giant form, so to speak." His experiments were performed in the following way: A piece of bread was soaked in feces containing eggs, embryos, or adult forms and introduced into the stomach of a frog, which was then placed in a compartment containing filtered water. A second frog was put in a second glass bowl in which glass slides smeared with infected feces were also placed. A third was kept as a control. Five series of three frogs were used and in the majority of these the results were identical. In the case of the first frog submitted to the infection by way of the stomach, which had swallowed three eggs already in advanced stages of segmentation, the animal died one and one-half months later. At the necropsy there was edematous infiltration of the abdominal wall and in the peritoneal cavity a small quantity of blood-stained fluid which, near the stomach, contained little red flakes; under the microscope these flakes were seen to consist of fibrin and red blood-corpuscles. It also contained three adult female forms of *Anguillula stercoralis* not fecund. Two were living, the third was dead. In the intestine only some infusoria were found. Examination of the lungs, heart, and other organs was negative. Teissier concluded from this experiment that eggs introduced experimentally into the stomach of frogs can live there and develop up to producing the adult stercoral form but without multiplying in the absence of males. He thought that these forms penetrated into and lived in the abdominal cavity. In the second frog, which had been infected with a crumb of bread containing eggs and *Anguillula* embryos, and which had died two months after the infection, no *Anguillula* parasites were found at autopsy, although there was a little blood-like fluid in the abdominal cavity. In the intestine there were some infusoria, but no other parasites. He thought that in this experiment the parasites had probably been killed by the gastric juice. The rest of the experiments were performed with frogs kept in bowls in which were also placed infected feces. With the exception of two of the animals, all died within one and one-half months. At necropsy Teissier found these parasites all through the digestive tract of the frogs, but particu-

larly in the large intestine. He also found them in the lungs. Their length varied from 8 mm. to 1 cm. One measured 12 mm. In width they measured 130μ on the average. In the bowls he found *Ang. stercoralis* of the human being, but never of the size of those present in the frog. In his control frogs, he never found the parasites. He concluded that a variety of *Ang. stercoralis*, found by him in a man suffering with diarrhea, can transmit itself to the frog, at the expense of which it can live and undergo a complete development in the intestine as well as outside of it; that when the parasite enters the frog it may become a giant *Anguillula*. He believed that the presence of *Anguillula* in the intestine caused the blood in the feces of the frogs, and that the hemorrhages in the intestinal walls were also due to their presence. He did not find the embryos in the circulating blood and conjectured that perhaps the capillaries were too small. Moreover, he states that the parasite is not an habitual hematozoan but rather a facultative hematozoan. Again, in a second patient coming from Madagascar suffering with diarrhea, he found the adult *Anguillula stercoralis* in the stools. Teissier in his paper does not mention *Angiostoma nigrovenosum*. It is not clear that he was not working with it, particularly as he found the parasites he describes in the lungs of the experimental frogs.

In 1897, Valdes (64) reported a case of infection with this parasite. The patient was well until 15 months before his entry to the hospital and had never been out of Spain. He began to grow pale and suffered from headaches and diarrhea. On admission he showed considerable anemia; occasionally there was abdominal pain without particular localization. Physical examination was otherwise negative. The diarrhea was intermittent. No blood was seen in the stools. The urine was normal. The blood examination showed considerable anemia with decrease in the number of red blood-corpuscles. In the stools were found large numbers of the embryos of *Anguillula*; from these Valdes obtained the adult forms in cultures. The author could account for the anemia and diarrhea of his patient in no other way except by the presence of the parasite. Under anthelmintic treatment the patient improved, and as the parasites diminished in numbers, the symptoms abated. When the treatment was stopped the patient became worse again. Valdes concludes that *Ang. intestinalis* may be a very

harmful parasite. The patient recovered under treatment with male fern, thymol, and santonin, and after 2 months was well. The author refers to the finding by Teissier of embryonic forms in the blood. He states that he was not able to find them, but that when he looked for them in the blood the case was so well advanced in convalescence that perhaps the opportunity had gone by.

In 1897, P. Barbagallo (65) reported the third case from Sicily. The patient had been sick for nine months without any apparent cause. He complained of pain in the umbilical region and right iliac fossa. His abdomen was slightly distended. He had obstinate diarrhea, alternating with periods of constipation, and complained of dizziness. The physical examination was negative. The blood examination showed a moderate leucocytosis. The stools were yellow-brown and pultaceous. They contained large numbers of *Anguillula* embryos. The patient was treated with ethereal extract of male fern freshly prepared, 2 grams being given daily. As a result the adult female forms came away. After 6 days' treatment only dead larvæ were found. On the 20th day no larvæ were demonstrable. With the diminution of the larvæ the dizziness and buzzing in the ears, etc., diminished and in a short time the patient was well established in health.

Having reviewed the literature in regard to the parasite, let us return for a moment to the question of the appearance of the embryos as hematozoa.

Sonsino as early as 1874 (1) thought that the larvæ of the *Uncinaria* might constitute the *Filaria sanguinis hominis* of Lewis; but afterward, finding that this position was not warranted by observed facts, receded from it. Later, Parona and Grassi (20) sought to establish this view. They argued that when near the second stage, during the process of change, the larvæ of *Uncinaria* have few marks of distinction in their structure to identify them, and that the same is true for *Filaria*. Again, *Filaria* is an embryo and is found in the same regions as *Uncinaria* and often in a similar class of cases, for example, in anemias. They thought that the larvæ might possibly pass into the blood through the damaged mucosa. When, however, one considers the size of the two parasites this idea would appear to be erroneous, as Perroncito had pointed out long before. It also occurred to

this latter author that *Strongyloides intestinalis* was a species of *Filaria* or *Strongylus* larva which went through the whole of its life up to the encapsulation in the human blood current. In 1876, however, Bancroft and Lewis described the adult parasite of *Filaria nocturna*, and from this fact and from Manson's work on *Filaria* in man, Perroncito finally concluded (rightly, as it would seem) that there was no relation whatever between *Strongyloides intestinalis* and *Filaria sanguinis hominis*. P. Teissier (62), however, as we have seen, took up this idea again and believes that *Strongyloides* is a facultative hematozoan.

We would once more point to the fact that we were never able to find nematodes in the blood of our patient, though they were often carefully sought for. In 4 other cases of infection with *Strongyloides intestinalis*, more recently encountered, we have never been able to find these nematodes in the blood in daily examinations extending over a considerable period of time. A microscopical study of the tissues of the small intestine does not allow us to conclude that the parasite passes into the circulating blood. Even if by accident one or two nematodes should by any accident happen to enter into a blood-vessel, there would be only the faintest chance of finding them in the circulating blood. It is unfortunate that Teissier did not attempt to grow his nematodes found in the blood on fecal material. In this way he might perhaps have been able to prove that they were not *Strongyloides* embryos. It is not clear that his case was not one of combined infection with *Filaria* and *Strongyloides intestinalis*, and we are compelled to take this view of it. We also think that in his studies with frogs the *Angiostoma nigrovenosum* was probably the "giant *Anguillula*" described by him.

Since coming to Manila we have had the opportunity of observing four other cases (in addition to our first case) of infection with *Strongyloides intestinalis*, one of which terminated fatally. In all there was a moderate anemia present and the counts of the leucocytes made once in three cases and twice in one case showed either a normal number or a slight increase.

All of these patients suffered from an intermittent diarrhea, often accompanied with gastro-intestinal disturbances. The stools contained many of the embryos, but in none of them were eggs or adult parasites of either generation found. The blood examina-

tions in all four cases were always negative for parasites. From cultivation of the embryos found in the stools from these cases we have been able to obtain adult males and females of the free-living generation; occasionally, however, the cultures skipped this generation and only filariform larvæ were obtained. A description of this free-living generation is therefore given.

In the free-living generation, when examples of both sexes are present, there are from 8 to 10 times as many females as males. The females are larger than the males; their bodies also taper more in the posterior portion. They measure generally from 1 mm. to 1.4 mm. in length and from .05 mm. to .075 mm. in breadth. In the adult free-living generation the esophagus has the same form as that of the larvæ, except that it shows a relatively smaller increase in length, measuring now about .16 mm. Of the three portions of the esophagus the buccalic is the longest. It measures 99 μ and represents in consequence a little more than half of the entire apparatus. The cephalic extremity is rounded and pierced by the mouth, about which, on careful examination, three or four papillæ can be made out. Next to the mouth comes a vestibule, which for a short length presents a gradual enlargement. It is much better developed than in the larvæ, and enters the anterior extremity of the esophagus which juts from its interior in the form of a smooth cone. This part of the esophagus is continuous with the bulbous or terminal portion, which encloses an apparatus for trituration consisting of three chitinous teeth in the form of a $\hat{Y}$. The intestine of the female is also somewhat longer than that of the male. It ends, as in the larvæ, in a teat at the right side of the body at the base of the tail, and often protrudes a little. On each side of the body, running longitudinally, can sometimes be counted from 16 to 18 cells, which are in close apposition, but which can be distinguished from one another by their nuclei. In the female the posterior extremity of the body stretches itself out into a tapering, thin, fine tail, often lightly coiled into a spiral. A little below the middle of the body and on the right side is the vulval opening marked by a slight contraction and giving access to a double uterus, the horns of which extend the one anteriorly, the other posteriorly. Each of these ends in an ovary. The eggs measure 70 by 45μ. They are elliptical; the shell is delicate and the vitellus contains a few granules. The eggs are often more or

less segmented when laid. Indeed, not infrequently they hatch in the body of the adult and one can then see the embryos moving within the body of the mother. As a rule, hatching is completed within 24 hours. At first the worms are thin, the tails are tapering, and the bulbous swelling of the esophagus and the chitinous teeth are apparent. They soon change, however, and become more like *Filaria*, that is, they pass from the rhabditiform to the strongyloid stage.

The free adult males differ in the following respects from the females: they are shorter and thinner, measuring from about .75 to 1 mm. long by .04 to .06 mm. wide. The esophagus is a little shorter than in the female. The caudal extremity measures about 70μ; it tapers quickly and is curved on itself in a manner quite different from the spiral coils in the tail of the female. Just at the base of the tail one can readily distinguish two cone-shaped and curved spicules, which represent the copulatory organ.

In our second fatal case associated with infection with this parasite there were found, at necropsy, miliary and conglomerate tubercles, as well as ulcerative and bronchiectasic cavities of the lungs. In addition there was an extensive catarrh of the duodenum and jejunum with much mucus, and beneath this a reddening of the intestinal mucosa. Microscopic sections of the small intestine showed changes similar to those already described in the first case.

In conclusion we may add that from the study of microscopic sections from our two fatal cases and from observations made upon our five clinical cases, we cannot regard the parasite as harmless; on the other hand we do not regard it as one particularly dangerous to man. We believe that it is capable of causing, clinically, an intermittent diarrhea with intestinal disturbances and, anatomically, a catarrh of the small intestine. It seems quite certain that the parasite causes some injury from its rapid mechanical movements; whether it also, through its metabolism, produces any chemical substance harmful to man has yet to be proven. The work of Peiper of Griefswald in regard to the giving off of poisons by a number of nematodes is well worthy of consideration. Moderately severe infections probably cause only slight disturbances.

Treatment.—The administration of turpentine has no apparent

effect upon the parasite. The milder cases of infection generally yield to large doses of thymol, especially when combined with general tonic treatment. It is often necessary to repeat the treatment at intervals. In the very severe infections neither male fern nor thymol are of any apparent value in curing the disease and ridding the patient of the parasite.

I wish to thank Professor Halsted for allowing me to report the first case and Dr. Charles Wardell Stiles, of the Bureau of Animal Industry, Washington, for verifying the diagnosis of the parasite in the first case and for several valuable suggestions.

Manila, P. I., August 10, 1900.

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DESCRIPTION OF PLATES II AND III.

Fig. 1. Adult *Strongyloides intestinalis* (parasitic form).

Fig. 2. Rhabditiform embryo of the adult seen in Plate I.

Figs. 3 and 4. Adult male and female of the free-living generation.

Fig. 5. Section of the duodenum showing the embryo lying beneath the epithelium of the villus.

Fig. 6. Section of the mucosa of the small intestine showing a portion of the adult female cut longitudinally.

Fig. 7. Section of the small intestine showing cysts, and embryos cut transversely, lying in the walls of the crypts of Lieberkühn. The crypt marked with a line — contains the embryos lying in the wall.

The photomicrographs are from the Army Pathological Laboratory, Manila.

NOTE.—Since the above article has been placed in type, a letter has been received from Dr. Strong announcing that monkeys have been successfully infected by feeding them the embryos of the *Strongyloides intestinalis* through a stomach tube. The animals suffered from diarrhea, and in their stools large numbers of the ova of the *Strongyloides intestinalis*, containing unhatched embryos, were seen. This is an important fact, because the ova are rarely seen in the fresh feces of men. Monkeys captured from a wild state have also been found to be sometimes infected with this parasite, which apparently produces in them the same changes as in man.

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April 20, 1901.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

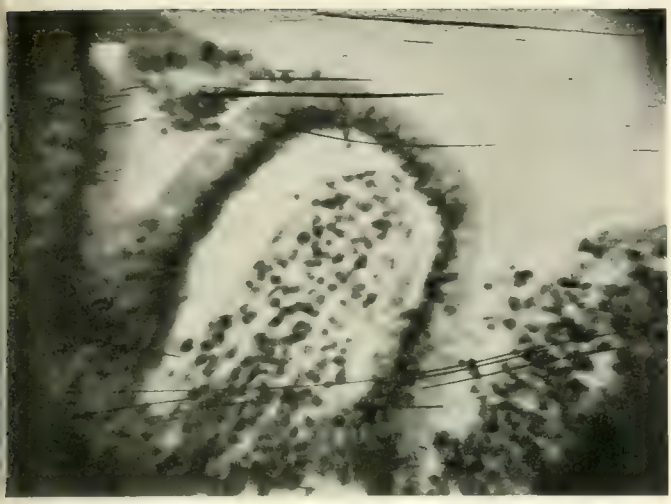

FIG. 5.

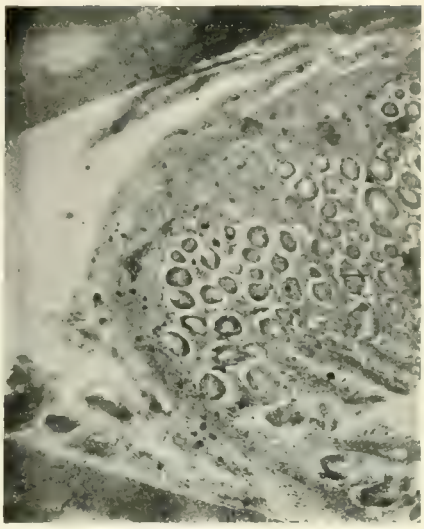

FIG. 7.

FIG. 6.

ON THE PATHOLOGICAL CHANGES IN HODGKIN'S DISEASE, WITH ESPECIAL REFERENCE TO ITS RELATION TO TUBERCULOSIS.

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(Plates IV–VII.)

Historical.—It is seventy years since Hodgkin[1] called the attention of the medical world to the peculiar enlargement of the lymphatic glands, which has since been designated by his name. Hodgkin's original paper was a simple report of seven unusual cases, which had come under his observation as pathologist at Guy's Hospital. He noted that the cases agreed in glandular tumors and were frequently associated with enlargement of the spleen. He did not attempt any critical analysis of his material, and undoubtedly had no conception that, in one or possibly two of his cases, he was dealing with a peculiar and rare disease. The other cases have no interest for us in this connection, as they are instances of tuberculosis, syphilis and possibly leukæmia.

In 1856 Wilks[2] described much more accurately several similar cases. His observations had been made independently of any knowledge of Hodgkin's work. A few years later,[3] he again published a series of cases, and included in his analysis the cases published by Hodgkin in 1832. His clinical descriptions are more complete and accurate than those of Hodgkin. We are left with a clear impression of the disease, as we know it to-day—a gradual progressive enlargement of the lymphatic glands, beginning usually in the cervical region and spreading throughout the lymphoid tissue of the body, and forming nodular growths in the internal organs, resulting in anæmia and usually a fatal cachexia. The absence of an increase in the white blood corpuscles was noted.

[1] Med.-Chirurg. Transact., 1832, vol. xvii, p. 68.
[2] Guy's Hosp. Reports, 1856, vol. ii, p. 114.
[3] Guy's Hosp. Reports, 1865, vol. xi, p. 56.

Wilks referred to the condition, in his second report, as "Hodgkin's disease," suggesting also the term "anæmia lymphatica" in contradistinction to "leucocythæmia lymphatica," which was at this time attracting much attention.

It is discouraging to find that in the years that have passed since these early observations our knowledge of the nature of the disease has not materially increased. Many cases have been reported and much has been written on the subject. Different writers, impressed by some one feature of the disease or some point of resemblance to other conditions, have confused the little knowledge we have by describing similar cases under different names. We have almost as many synonyms for Hodgkin's disease as we have important publications. Progressive multiple lymph-gland hypertrophy (Wunderlich, 1858),[4] lympho-sarcoma (Virchow, 1864),[5] pseudoleukæmia (Cohnheim, 1865),[6] adénie (Trousseau, 1865),[7] multiple lymphadenoma without leukæmia (Wunderlich, 1866),[8] malignant lymphoma (Billroth, 1869),[9] are well-known terms which explain themselves. It is unnecessary here to discuss the various points raised by these different observers. It is sufficient to state that during the twenty years following Wilks' report, the general conception of Hodgkin's disease was: a constitutional disorder resulting in a hard or soft form of lymphoma, marked clinically by large tumors of the lymph glands, enlargement of the spleen, anæmia without leucocytosis, fever and a fatal cachexia; histologically by a simple hyperplasia of some or all of the lymph glands and nodules of lymphomatous tissue in the internal organs.

The malignant nature of the growth was frequently upheld, but it was usually considered to be neither true neoplasm nor infectious process, but a constitutional disturbance.

In 1885-7, Pel[10] and Ebstein[11] described cases of enlargement of the lymph glands with recurring fever, and considered that

[4] Archiv f. physiol. Heilk., 1858, Bd. xvii, p. 122.
[5] Die krankhaften Geschwülste, Berlin, 1864, Bd. ii, p. 728.
[6] Virchow's Archiv, 1865, Bd. xxxiii, p. 451.
[7] Clinique Med., 1865, Tome iii, p. 555.
[8] Archiv der Heilk., 1866, Bd. vii, p. 530.
[9] Gen. Surg. Path. and Therap., 1869 (translation of 4th German edition).
[10] Berliner klin. Woch., 1885-1887, Bd. xxii, p. 3; vol. xxiv, p. 644.
[11] Berliner klin. Woch., Bd. xxiv, pp. 565; 837.

this constituted sufficient ground for a separate division of pseudoleukæmia, for which Ebstein suggested the name of "chronic relapsing fever." A similar case had been described previously by Murchison,[12] and since Ebstein's article several like observations have appeared in the literature. Musser, in a recent article, has reviewed the whole subject.[13] We are in serious doubt about the true nature of such cases. It is well known that intermittent pyrexia occurs in sarcoma and occasionally in tuberculosis, and is attributed to an acute infection. It is undesirable to make clinical divisions of a disease without a pathological foundation.

The last epoch in the history of Hodgkin's disease extends from about 1887 to the recent paper of Clarke.

Delafield,[14] in 1887, published a case of primary tuberculosis of the lymph glands, simulating pseudoleukæmia. A similar case had been described by Hilton-Fagge[15] in 1874. Askanazy,[16] Weishaupt,[17] Cordua,[18] Courmont, Tixier, Bonnet[19] and others have since then published similar observations. This re-awakened the old question as to whether we could attribute Hodgkin's disease to the action of the tubercle bacillus. It was well known that many cases terminated in tuberculosis.

Waetzoldt,[20] Brentano and Tangl,[21] Cordua[22] and Ricker[23] recorded such cases. Sternberg,[24] in his extensive research on this subject, found tuberculosis in eight out of thirteen autopsy cases of Hodgkin's disease and concluded that he was dealing with a peculiar form of the tuberculous process. His article has had

[12] Trans. Path. Soc. of London, 1870, vol. xxi, p. 372.

[13] American Medicine, 1902, vol. iii, p. 13.

[14] Medical Record, 1887, vol. i, p. 424.

[15] Path. Trans., 1874, vol. xxv, p. 235.

[16] Ziegler's Beiträge, 1888, Bd. iii, p. 411.

[17] Pseudoleuk. u. Tuberculose, 1891. Inaug. Dissert., Tübingen.

[18] Beiträge zur Kenntniss der tuberculösen und lymphomatösen Veränderungen der Lymphknoten. Arbeiten a. d. pathol. Institut in Göttingen, 1893, p. 152.

[19] Journ. de Physiol. et Path. Gen., 1899, vol. x, p. 827.

[20] Centralblatt f. klin. Med., 1890, Bd. ii, p. 809.

[21] Deutsche med. Woch., 1891, Bd. xvii, p. 588.

[22] Loc. cit.

[23] Archiv für Chir., 1895, Bd. l, p. 573.

[24] Zeitschrift für Heilkunde, 1898, Bd. xix, p. 21, and Centralblatt f. d. Grenzgebiete d. Med. und Chir., 1899, Bd. ii, pp. 641; 711; 770; 813; 847.

great influence. Ferrari and Cominotti,[25] Crowder[26] and others have described Hodgkin's disease associated with tuberculosis and agreed with Sternberg's conclusion on the relation between the two diseases. The opposing view upheld by Weishaupt,[27] Westphal,[28] Dietrich,[29] Fischer,[30] etc., although based on stronger reasons was overlooked.

The enthusiastic reception of such a relationship has now waned. The great liability of cachectic individuals to tuberculosis, and the number of negative cases have re-established the independence of Hodgkin's disease. Clarke,[31] in a recent article on the subject, sums up the present opinion in concluding that there is no warrant for the view maintained by some writers that the disease is merely a lymphatic tuberculosis.

The present tendency is to describe all overgrowths of lymphoid tissue under some general term, such as lymphadenoma, lymphoma or adenia, excluding inflammatory enlargements. This is a natural reaction from the arbitrary subdivisions of the subject, which have been made on clinical grounds alone. Cohnheim and Wunderlich were among the early writers who considered pseudoleukæmia and leukæmia as different stages or manifestations of the same process. This view has prevailed from time to time, and has lately been reagitated.

In concluding this historical résumé, it would seem evident that much confusion has arisen from the numerous synonyms employed. The most appropriate term seems to be a matter of personal opinion. It is unfortunate that the word "lympho-sarcoma" was ever used in this connection, as it has led to confusion with primary sarcoma of the lymph glands, which is a very different affection. The term "Hodgkin's disease" has the priority and the weight of long established usage. It has the merit of leaving open the question of the exact nature of the pathological process. We would do

[25] Wiener klin. Rundschau, 1900, Bd. xiv, p. 1035.
[26] New York Med. Journal, 1900, vol. lxxii, p. 445.
[27] Loc. cit.
[28] Deutsche Archiv f. klin. Med., 1893, Bd. li, p. 83.
[29] Beiträge zur klin. Chir., 1896, Bd. xvi, p. 376.
[30] Archiv f. klin. Chir., 1897, Bd. lv, p. 487, and Deutsche Chirurgie, 1901, Lieferung 24a.
[31] Brit. Med. Journal, 1901, vol. ii, p. 701.

well to confine ourselves to the use of this old word as the name of a specific pathological and clinical condition until we are better informed concerning the nature of the disease, and can give it a satisfactory etiological or anatomical title.

Etiology.—*Two etiological possibilities* in the case of this disease have each been warmly advocated, viz.: that of a malignant growth or that of an infectious process.

Clinically, there seems to be more evidence of its being of the nature of an infection. The course of the disease, though usually chronic, may be acute. We frequently have fever associated with other septic symptoms; analogous conditions are found in septicæmia and cachexias due to pyogenic organisms. The frequency with which the disease starts in the cervical region has suggested to many a probable source of infection in lesions of the mucous membranes or skin. Macroscopically, the growth differs from malignant tumor in the absence of capsular infiltration and implication of the adjacent tissues. Sarcoma does not confine its growth to gradual extension from gland to gland. We do not know of any malignant neoplasm the metastases of which occur only in one form of tissue. Hodgkin's disease seems not to metastasize by cellular transplantation but by causing a proliferation in pre-existing lymphoid tissue, apparently anywhere in the body.

Histologically, it might be thought that the changes resemble those of a malignant growth, but we believe that closer study will show a greater similarity to inflammatory processes.

The bacteriological findings in the disease are incomplete and unsatisfactory. The ordinary pyogenic cocci and several unidentified organisms have occasionally been obtained from the blood of patients suffering with the disease and from the glandular growth before and after death. In the variety of organisms which have been isolated by different observers,[32 33 34 35] we find the surest proof that as yet the true etiological factor, if it is a microorganism, is undiscovered. We are not ready to accept the sug-

[32] Verdelli, Centralbl. f. d. med. Wissenschaften, 1893, No. 33, p. 545; Centralbl. f. innere Med., 1895, Bd. 16, p. 24.

[33] Brigidi d. Piccoli, Ziegler's Beiträge, 1894, Bd. 16, p. 388.

[34] Rudler, De la lymphadénie, 1895. Thèse de Lyon.

[35] Delbet, Compt rendu de l'Acad. des Sciences, 1895, No. 24.

gestion, that, here, we have a pathological process which can be excited by a number of different micro-organisms. The work done is too full of error, and the possibility of a terminal infection, or of post-mortem invasion, too well known for us to consider these observations as conclusive.

In contrast with these confusing and varied results, we find satisfaction in Fischer's[36] report on the subject. In twelve cases examined, he found blood cultures sterile, cultures from extirpated glands sterile, and animal inoculations all negative. In one case, in which there was a relapsing fever, the blood cultures made during the periods of apyrexia were always negative, but during the periods of fever organisms were present in the blood. This would suggest that such exacerbations of temperature in this disease are due to secondary infection.

One possible instance of the contagious nature of the disease is cited by Murray,[37] but the possibility of mere coincidence must not be forgotten. This is also true of the question of hereditary influence. Instances of such relationship are also few in number.

The influence of combined tuberculosis and cancerous heredity is dwelt on by Hutchinson,[38] with far reaching but not convincing conclusions.

In but one case do we know of lymphomatous nodules being produced in animals by inoculation with a micro-organism, isolated from a case of Hodgkin's disease. Delbet's communication, though interesting, needs confirmation.

Although many diseases have been brought forward as etiological factors in Hodgkin's disease, as our knowledge has increased, there has been little difficulty in eliminating any causal relation between Hodgkin's disease and all other diseases with the exception of leukæmia and tuberculosis.

Before Virchow's paper, in 1845, we cannot expect to find any differentiation between enlargement of the lymph glands with or without blood changes. In looking over the reports of these early cases, we often feel that the diagnosis of leukæmia would be made with our present knowledge of the blood picture.

[36] Loc. cit. [37] Allbutt's System of Medicine, vol. v, p. 587.
[38] Archives of Surgery, 1897, vol. viii, p. 145.

There has been considerable tendency recently to drop the terms leukæmia, pseudoleukæmia, lympho-sarcoma, etc., and return to the classification of lymphatic enlargements under such a general term as adenia or lymphadenoma. The objection raised is that we are giving to subdivisions of the groups names which are only descriptive of some peculiar condition which may not constitute a separate class etiologically. In support of this view, cases of leukæmia are cited where the peculiarity of the blood picture varied, developing or disappearing under observation.

We sympathize heartily with the objection in so far as it applies to the use of separate names for clinical features of a disease. A historical retrospect of this disease shows to what confusion the indiscriminate application of descriptive terms may lead. These authors,[39] [40] who wish to simplify the subject, do not seem to recognize the fact that the leukæmias and Hodgkin's disease or pseudoleukæmia present entirely different and specific microscopic pictures; and that on the basis of these anatomical differences we have every right to classify them as separate and distinct diseases. We agree with them, however, in asserting that a blood change is a slight and often variable feature upon which to base a diagnosis. The pathological lesions inducing such a change must be the real point of differentiation, although the great aid and importance that a thorough study of the blood may furnish is not to be underestimated. We may note here that Pinkus[41] seems to place undue stress on the value of a blood change in Hodgkin's disease. He considers a relative lymphocytosis as the chief diagnostic point, and is willing to call pseudoleukæmia any enlargement of the lymph glands consisting of a simple hyperplasia, with a relative lymphocytosis, without a marked increase in white blood elements. Only the record of a number of cases can establish the frequency of lymphocytosis in this disease, but the glandular enlargement cannot be one of simple hyperplasia, if it is Hodgkin's disease. The histological changes in this disease are quite different from those in lymphatic leukæmia.

Tuberculosis has been the chief source of confusion in the con-

[39] Martin and Mathewson, Brit. Med. Journal, 1896, vol. ii, p. 1634, 1701.
[40] Spencer, Lancet, 1897, vol. i, p. 648, 721, 792.
[41] Nothnagel, Spec. Path. d. Therapie, 1901, vol. viii, p. 81.

ception of Hodgkin's disease as a separate pathological condition. Tuberculosis confined in the main to the lymphatic glands, and general tuberculosis with involvement of the glands, have both been causes of error.

Clinically, there may be great similarity between these two diseases. We have in both an enlargement of the glands, beginning most frequently in the cervical region and extending through the other lymphatic groups. In location, size of the glands, age of the patient, resulting anæmia and cachexia, accompanying fever or the fatal termination there may be no essential difference in the two conditions. There may be no ulceration or necrosis or signs of tuberculosis in other parts. Macroscopically, the glands may appear alike to the casual observer. The massing together and the fusing of the different glands, from the disease breaking through the capsule, usually occur, however, in a large tuberculous growth. Necrosis and caseation are the rule in tuberculosis, and are never present in such marked degree in Hodgkin's disease, unless there is a secondary infection. Fibroid changes occur in both diseases. The other form of tuberculosis, not a general adenitis but a formation of miliary tubercles, is not likely to be mistaken either microscopically or macroscopically. The greatest confusion has occurred when in glands the seat of a true Hodgkin's disease tuberculosis has supervened. Then we may have the macroscopic features of the two processes in different sets of glands or in the same gland.

Histologically, tuberculosis of the glands, if appearing alone, is relatively easy to recognize; we expect either miliary tubercles or general inflammatory changes in the gland, with typical caseation accompanied usually by Langhans' giant cells and tubercle bacilli. The bacilli in some cases, especially if very old, are said to be extremely difficult to demonstrate. Similarly, Hodgkin's disease by itself, we hope to be able to show, is easily identified. In poorly prepared or carelessly studied specimens, the peculiar histology of Hodgkin's disease is easily overlooked when typical caseation, or giant cells, or tubercle bacilli are found. We are confident that if Hodgkin's disease exists in a gland, the histology will give evidence of it, and that tuberculosis has no other relation to it than frequent association, and that the two lesions can always be separated, unless the tuberculous process has gone so far as practically to destroy the tissue.

The cases in the literature, when there is a question of the two diseases, have been explained in one of three ways. In the first place, tuberculosis, which has been found either by the microscope or by experimental inoculation, in Hodgkin's disease, is assumed as the cause of the disease, or to put it in another way, it is tuberculosis masquerading as Hodgkin's disease; or the tuberculosis is considered as associated or combined with Hodgkin's disease, this disease being held as a separate malady; or finally the tuberculosis is held as simply a terminal infection in Hodgkin's disease, as it is so frequently in the other severe cachexias. The number of such cases on record is very large. The subject has been dealt with extensively in recent years, especially by Westphal, Dietrich, Fischer, Sternberg, Crowder and Clarke.

Sternberg, in an article which appeared in 1898, gives a very complete description of the pathological findings in a series of fifteen cases, thirteen of which were supposed to be pseudo-leukæmia. The clinical histories are meagre. The histological peculiarities of the growth, from his descriptions and illustrations, agree closely with the changes met with in our series of cases, and represent, we believe, a specific pathological process.

In eight of the thirteen cases, tuberculosis was demonstrated in one or more organs. He concluded from this that in this series he was dealing with a chronic inflammatory process due to the action of the tubercle bacillus. True Hodgkin's disease he considers to be microscopically a simple hyperplasia or hypertrophy of the lymphoid tissue, basing this conclusion on the examination of one autopsy case.

We cannot agree with this statement, nor understand his conception of a peculiarity of the virus of the tubercle bacillus, which he suggests as the cause of such a growth. It is difficult to assume a new tuberculous process of such a limited character and one hitherto unknown. Also we cannot explain why in many of the cases no definite evidence of tuberculosis or the tubercle bacilli can be demonstrated.

Fischer, in 1897, in a short and concise article, had already settled the discussion to our satisfaction. He offers twelve cases of lymph-gland hypertrophy in which a similar specific histology was apparent. We regret he did not enter more fully into the

microscopic details. Blood cultures and inoculations into various laboratory animals in each case were negative. There was no increase in the leucocytes. Four of the cases came to autopsy with general metastases. In two of the cases there was tuberculosis, evidently recent and presumably a terminal infection. The inoculation experiments with these two tubercular cases had been performed fourteen weeks and fourteen days respectively before death, and gave, as already stated, negative results. This proved that there was then no tuberculosis in the lymph glands, although there was an associated tuberculosis in the internal organs.

His conclusions are just and now generally accepted—that malignant lymphoma is a distinct well characterized disease, in which tuberculosis often occurs secondarily. However, we do not also agree, that animal inoculation, as well as microscopical examination, is necessary for diagnosis in doubtful cases.

Dietrich, in a very able critical article in 1896, had come to similar conclusions. He defines three possible relations between tuberculosis and malignant lymphoma—an occurrence of the two diseases in the same case but in different organs, an association of the two diseases in the lymph glands, and a simulation by generalized lymph-gland tuberculosis of the clinical picture of pseudoleukæmia. He very correctly bases his diagnosis of malignant lymphoma upon the histological changes, and gives a correct if somewhat brief description of the findings in two cases, which he reports for the first time.

The outcome of all this discussion seems to be that tubercle bacilli may be present in a malignant lymphomatous process, without any primary etiological connection between the two, and also that there may be advanced tuberculosis present in a case of malignant lymphoma without the presence of tubercle bacilli in the gland.

Case I of our series is exactly similar to those of Sternberg and other writers on the subject. Here we have a case of Hodgkin's disease of four years' standing, ending in tuberculosis. The symptoms suggesting tuberculosis appeared only during the last month. The histological picture of the lymphomatous changes in the glands, spleen and liver is complicated by the associated tuberculosis, but the two processes are easily distinguished.

It would be interesting to observe the action of tuberculin in a

series of cases of Hodgkin's disease; in five of our cases in which it was used the result was negative.

Clinical Characters.—In summarizing the clinical features of Hodgkin's disease from the numerous cases reported in the literature, we at once meet with the difficulty that many instances of entirely different affections have been included and described under this name. The descriptions of early writers on the subject are quite as clear and complete, as those we find in the recent literature, and there is not the same tendency to make some one clinical feature the predominating characteristic. Von Winiwarter,[42] in 1875, gave an excellent account of the disease. Gowers'[43] description is also well known. The recent article by Fischer contains a very complete review of the subject.

The important features which should be considered in a case are briefly as follows: The disease occurs in more than half of the instances in early life; probably the majority of cases are in children. Males are much more frequently affected than females. The general health of the patient before the onset of the disease is usually excellent. We do not find a tuberculous family history in an unusual percentage of the cases.

Throat trouble and inflammation of the ear or eye often precede the growth.

The one constant feature of the disease is the progressive enlargement of the lymphatic glands. This almost always begins in the cervical region. We know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis, in which the disease commenced elsewhere. The enlarged glands are usually at first unilateral, although later the opposite side of the neck is frequently affected. The disease affects progressively the neighboring glands, apparently following the normal lymphatic distribution. The glands form at times enormous tumor masses, which usually present the following characteristics: even in the large masses discrete glands can be mapped out, the enlargement persists or steadily increases, variations in size are not met with as a rule, retrogressive changes and involve-

[42] Archiv f. klin. Chir., 1875, Bd. xviii, p. 98.
[43] Reynold's System of Med., 1880, vol. iii, p. 529.

ment of the skin or adjacent tissue is never apparent unless there is a secondary infection.

During the first stage of the disease, which may be prolonged over months, the general physical condition is apparently normal, even while the glands are increasing rapidly.

The second stage of the disease, marked by progressive asthenia, cachexia, and anæmia, invariably develops, usually after one or more years, but occasionally after a very brief period of glandular growth.

The anæmia, which is usually well marked, is of the secondary type. No increase in the leucocytes is observed unless there is an acute infection. A relative increase in the number of the lymphocytes does occur in some cases but is not invariable. We believe it depends on the stage of glandular growth. Sudden temporary changes in the number of leucocytes are recorded, and may be explained in several ways, as will be stated later. Irregular or continuous fever is the rule, attributable to the inflammatory nature of the disease. Intermittent or recurring fever, which occasionally occurs, depends, presumably, on repeated secondary infections.

In this stage of the disease all the large glandular groups may be involved; the extent of the process seems to be limited only by time. The disease rarely progresses further than the abdominal glands, the glands of the groin not being usually extensively enlarged. Enlargement of the spleen is almost always apparent, and may be enormous. The liver is less often enlarged. Pressure symptoms from the tumor masses about the trachea, blood-vessels and ducts of the internal organs are frequently observed, resulting in dysphagia, local or general œdema, jaundice, etc.

The majority of cases last from one to four years. Very acute and protracted cases are recorded, but are of a doubtful nature. The disease is apparently uniformly fatal. The commonest form of death in Hodgkin's disease is by tuberculosis, although many cases terminate, as in all cachexias, with symptoms of involvement of the lungs and general anasarca, without such an infection.

No therapeutic measure has been discovered which influences, either constantly or permanently, the course of the disease.

Extirpation of the glands is usually followed by a recurrence of

the enlargement, after a varying period of time. The secondary growth is frequently more extensive than the original tumor. Even if it were possible to remove all of the affected tissue, until we know the source of the infection, we cannot expect surgical measures to be of much avail.

PERSONAL OBSERVATIONS.

In looking over the surgical specimens, and the autopsy material of cases which were considered to be Hodgkin's disease, or suggested such a diagnosis, we were fortunate in finding eight cases, which closely resemble each other clinically and which on careful study were found to present a peculiar and, we believe, typical histological picture.

In the search for this material, we examined many specimens of true malignant disease, leukæmia, and tuberculosis. In none of these did we find similar macroscopic and microscopic changes in the glands. The study was suggested by the autopsy of a case of Hodgkin's disease (Case I), which had been under observation for three years. This boy died of tuberculosis.

We wished to ascertain, if possible, the nature of Hodgkin's disease, and its relation to tuberculosis.

These cases were treated in the medical and surgical wards of The Johns Hopkins Hospital. Our thanks are due to Dr. Osler and Dr. Halsted for the use of the clinical material.

Analysis.—Of these eight cases, seven were white and one colored. Seven of the cases were in boys under seventeen years of age, two of them were only five. The one woman in the series was fifty-five years old. A family history of tuberculosis was obtained in two cases, in five cases it was denied.

The initial growth was in the cervical region in all but one case; in this the first nodule was noticed in the episternal notch. In all of the cases the large, external tumor masses were in the cervical region. The right side of the neck was involved in four cases, the left in three cases, and both sides in one case. The primary glandular tumors were always of considerable size. The girth of the neck in one case was 50.5 cm., and the tumor mass weighed 2000 grams. The glands on the side of the neck, opposite the main growth, were noticeably enlarged in three cases.

The axillary glands were usually enlarged on the side of the tumor, the inguinal glands were not markedly increased in size in any instance.

The duration of the growth varied from two to seven years. In four of the cases the rapidity of growth had become greatly increased during the last months.

Two of the patients entered the hospital in a moribund condition; the general health of the other cases, when first observed, was fair.

All the patients appeared somewhat anæmic. There was a grave anæmia of a secondary type in two of the cases. The leucocytes, which were counted in seven of the cases, never showed

TABLE OF BLOOD COUNTS.

	Red blood corp.	Leucocytes.	Hb.	Differential Count.					Ratio of W: R	Abs. no. lymphocytes.
				P.m.n.	S.m.n.	L.m.n.	T.	E.		
Case i	4,124,000	12,500	63%	50	36.8	3.4	5.4	4.4	1 : 330	4600
		8,800		56.7	29.2	9.2	2.9	2.9	1 : 624	2570
	3,872,200	6,200	51%	74.6	22.4	3.2	.7	.05	1 : 267	1389
	2,670,000	10,500	55%							
Case ii....	4,784,000	10,500	65%	84	14	.8	.6	.4	1 : 455	1470
Case iv...	5,000,000	15,500	60%	87	2	4	1.6	3	1 : 322	310
	5,264,000	10,000	84%	77.6	9.4	10	1	2	1 : 526	940
Case v....	4,896,000	12,000	70%	80.8	13.6	1.6	2.4	1.6	1 : 408	1632
	4,984,000	8,200	80%							
Case vi ...	3,300,000	11,000		Reported normal.					1 : 300	
Case vii...	3,232,000	14,000	55%	46.4	38.6	2	7.8	2	1 : 210	5304
Case viii..		8,000		74	10	11		5		

any relative increase; the ratio between the red and white corpuscles was usually diminished. Differential counts were made in seven of the cases. In two of these there was a relative and absolute increase in the number of small mononuclear leucocytes. In two other cases these cells were noticeably few in number. Otherwise the blood counts were normal.

The spleen was palpable in three cases, and in one case the liver was considerably enlarged.

The growths were never painful. In one case, which proved fatal, there was dysphagia, and œdema of the arm from pressure of the tumor mass.

All of the cases showed a slight irregular fever, with occasional

exacerbations. One case gave a history of recurring fever with chills and sweats.

Tuberculin was given in five of the cases but without reaction.

There was no marked improvement in the condition of the patients under treatment with Fowler's solution internally.

Complete excision of the tumor mass in the cervical region was performed in five cases. An extensive recurrence appeared in one case within two years, and the glands were again removed. In another case, there was a second operation to remove a few glands, which had enlarged during eight months. One patient was lost sight of, and no statement as to recurrence can be made. One case died seven weeks after the operation with dropsical symptoms. The remaining operative case died in three months with extensive recurrence of the growth.

Inoculation experiments were made three times. In the case that died of tuberculosis, a rabbit inoculated with a piece of the gland died of tuberculosis in thirty-one days.

Subcutaneous inoculation of a rabbit with a gland from another case, resulted in the death of the animal in eight weeks. No apparent cause of death was made out. Material from a third case has been used to inoculate rabbits and guinea-pigs. One rabbit lived after subcutaneous inoculation over four months and was then killed. There was no diseased condition present attributable to the operation. Two guinea-pigs, one inoculated subcutaneously and the other intraperitoneally died in about five weeks. The autopsy failed to reveal the cause of death. Cultures made from this last case were sterile.

Five of the series terminated fatally, and three came to autopsy. The evidences of a marked cachexia with dropsy were present. In one case there was a generalized miliary tuberculosis, which from the history was apparently a terminal infection. No sign of tuberculosis was found in either of the other autopsy cases, or in any of the extirpated glands, although careful search was made in smears and sections for tubercle bacilli. The cervical, mediastinal, bronchial and abdominal glands were affected in the three autopsy cases. Metastases were present in the spleen in three cases, in the liver in two cases, in the pericardium in one case. In no other organs were lymphomatous nodules found.

The bone-marrow was not examined, as no material was saved. In connection with the relation to leukæmia, it would be most interesting to have a careful study of the changes in the bone-marrow in Hodgkin's disease. From the literature it would seem that lymphomatous nodules, such as appear in other parts of the body, may occur here.

Macroscopically, we have, in these eight cases, enlargement of the lymph glands characterized by the following points. The glands tend to remain discrete, even after they have reached individually an enormous size. This is due to the fact that the capsule is not infiltrated to any extent by the disease. The growth is therefore freely movable from the skin and adjacent tissues. The consistency of the glands varies greatly. The smaller glands, which presumably represent an earlier stage of the disease, are usually somewhat soft and elastic; the larger glands may be quite firm and hard. Glands of different consistency are usually present in the same growth. There are no large areas of degeneration perceptible unless there is necrosis due to a secondary infection.

On section the glands present several aspects. In the older growths we find an appearance somewhat suggesting the gross findings of carcinoma. We find a semi-translucent greyish surface, broken by intersecting opaque, yellowish lines. No cylinders of cells, however, can be expressed. The yellowish areas represent the fibrous tissue, which has penetrated throughout the gland substance and has undergone degenerative changes.

The younger growths show usually a uniform greyish surface, slightly more opaque than normal and bulging on section. Hæmorrhagic points may be present, but are often due to manipulation.

The metastases in the viscera present a similar appearance. They are of various size, from pinpoint to large nodules. They are usually of a greyish-white color, and sharply marked off from the affected tissue. Their outline however is irregular, and they appear to invade the organ in different directions. On section, they present the various appearances described in the glands.

This description, we believe, agrees completely with the generally accepted gross findings in Hodgkin's disease.

So-called metastatic nodules, apparently, may appear anywhere in the body where lymphoid tissue is found normally. They have

been reported in most of the internal organs, the muscles and the bone-marrow. Lymphoid nodules in the skin described in "lymphoderma perniciosa" (Kaposi), etc., are presumably an entirely separate affection.

Microscopically these cases, although apparently quite variable, always represent, we believe, some stage in the same general process. In the smallest gland examined, which was under two mm. in length, we found only proliferation of the flat, so-called endothelial cells which cover the reticulum of the lymph sinuses, and of the large cells of the centres of the lymph nodes, which are presumably identical cells. Mitotic figures in cells of this description are frequently seen. Dilatation of the blood-vessels and the lymph sinuses is usually a marked feature of the early stage. As the process advances, we find the lymph sinuses and the reticular spaces filled with masses of lymphocytes and proliferating endothelial cells. The presence of these newly formed cellular elements destroys the normal appearance of the gland by obliterating the distinction between the follicles and the sinuses. An occasional lymph follicle is now the only clue left to the original organ. The endothelial cells, which show many karyokinetic figures, in proliferating form large epithelioid cells with vesicular nuclei. Numerous giant cells with one or more nuclei and prominent nucleoli appear in great number. These give evidence in their structure and situation of being derivatives from the epithelioid cells and, in places, they are the most prominent feature of the specimen. Occasionally a very large giant cell with many small nuclei peripherally arranged is seen. These arise in an entirely different manner. The lymphoid cells, which are in the early stages very numerous, are of the usual small type. We consider that these cells also are derived from proliferation of the endothelial cells.

Plasma cells are often observed in almost as great numbers as the lymphocytes. Eosinophiles are usually abundant throughout the tissue spaces except in the germinal centres of the follicles. In two of our cases, both of them fatal, there were very few eosinophiles to be seen.

As the process advances the connective tissue shows marked proliferation. The framework of the gland becomes increased, and bands of connective tissue, starting often from about the ves-

sels, gradually break up the gland substance into course lobules, The connective tissue increase is at the expense of the other cells, and we find fragmentation of many of the nuclei of the lymphocytes and plasma cells. The tissue, which before had been so rich in cells, now undergoes a fibrous transformation. The process may continue until the coarse bands of connective tissue are more prominent than the small cellular islands which they include.

The capsule of the gland usually shows no change, except possibly some thickening. The blood-vessels, which are numerous and full of blood in the early stages of the disease, are often obliterated, as the fibrous change increases, by a periarterial thickening. We never noticed especial proliferation of the endothelium of the vessels. The coarse connective tissue bands are usually poor in cells, and may show a hyaline transformation.

Large areas which we can only explain as anæmic necroses are frequently observed. The centres of such foci show completely degenerated cells with fragmented nuclei. Surrounding the foci is the connective-tissue framework, showing hyaline changes. The free cellular elements have usually disappeared. Polymorphonuclear leucocytes are found infiltrating such areas, but not in great numbers. No micro-organisms were demonstrated.

It is evident that a gland examined at varying periods in the process would appear very different to casual observation. In the early stages we have a very cellular tissue, in which the predominating element is the lymphocyte. This represents presumably the soft type of the disease and we can understand why Hodgkin's disease is usually spoken of as a simple hyperplasia of the lymph gland. The fibrosis of the later stage represents the "hard type," and the connection between the two is not at first obvious. The process in its early stage has been frequently confused with sarcoma, and in the later stage with tuberculosis.

Consideration of the different cell types present.—Studies of the histogenesis of the lymph gland,[44] reveal the origin of the cells forming the fibrils of the reticulum, and of the cells which become flattened out to line the tissue spaces or lymph sinuses of the gland in the same embryonic mesenchyme cell. These so-called endothelial

[44] Gulland, Journal of Path. and Bact., 1894, vol. ii, p. 447.

cells and the large cells lying free in the tissue spaces of the lymph nodes, are apparently similar cells, the latter having simply lost their protoplasmic processes, and being free from any connection with the reticulum. These free cells, or mother cells of the germinal centres of the lymph nodes, were shown by Flemming[45] to furnish by their proliferation the small lymphoid cells of the gland. Presumably most of the small, uninuclear cells of the blood arise in this way. We have, then, in the connective-tissue cells of the reticulum, the endothelial cells lining the lymph sinuses of the gland, the larger lymphocytes or mother cells—different stages of differentiations of the same embryonic spider cell. It is important to bear this relation in mind in considering the origin and characteristics of the different cells in Hodgkin's disease.*

The abundance of *connective tissue* which appears very early in the process and becomes marked in the later stages arises from the proliferation of the connective tissue about the blood-vessels and from the trabeculæ of the gland, from the pre-existing reticular cells, and, we believe, in part, from a transformation of the proliferated endothelial cells into fibrous tissue. These *so-called endothelial cells* we do not believe are identical with the endothelium of the blood-vessels and the large afferent and efferent lymphatic sinuses, which form a regular membrane with specific functions. They are, in reality, only a species of flattened-out connective-tissue cells lining tissue spaces. Karyokinetic figures were frequently observed in these cells. In proliferating, they form epithelioid cells, having large vesicular nuclei, with a heavy chromatin network and one or more nucleoli. The cell body varies in form, it may be round or elongated, or have protoplasmic processes. The protoplasm may be clear and homogeneous or granular. Yellowish pigment has been seen in these cells.

The *large giant cells*, which are the most striking feature of these specimens, are evidently formed from these proliferating 'endothelial' cells. Transitions from epithelioid cells to large uninuclear cells, and from these to giant cells with one or more nuclei can be easily found. These giant cells usually lie free in the inter-

[45] Flemming, Archiv. f. mikr. Anat., 1885, Bd. xxiv, p. 50.

* The histological research of Dr. Florence R. Sabin on the development of the lymphatic glands has been of great value and assistance in this matter. Dr. Sabin's work is as yet unpublished.

stices of the tissue, but we occasionally see them on the reticulum, and with irregular protoplasmic processes. They occur in great number in the large lymph sinuses of the gland, and occasionally appear in the blood-vessels. They vary from the size of two or three red blood corpuscles to cells twenty times this size. The smaller cells are usually round or somewhat polygonal in shape, the larger cells are very irregular in outline. These cells have been frequently seen much elongated, passing between other cells, and in one specimen such a cell was found apparently going through a vessel wall.

The nucleus is always large in proportion to the size of the cell. It may be single or multiple. If single, it is usually round. Bean-shaped and irregularly indented nuclei are common. If multiple, the nuclei may be arranged peripherally in the cell, or heaped in the centre. Eight or ten nuclei have been seen in a single cell. The chromatin network is prominent in these nuclei, and one or more large nucleoli are always present. The nucleoli are usually oval, but they may be of any shape. The nucleoli always take a contrasting stain to the nucleus in the double stains, they have an affinity for acid dyes. No definite mitotic figures were ever seen in these cells. Direct division was frequently observed. The protoplasm is usually homogeneous, and stains well. It may appear granular, show vacuolization, or contain fat or pigment granules. Cells having bizarre and irregular nuclei are found in the oldest growths. These giant cells, so far as our observation reaches, are peculiar to this growth, and are of great assistance in diagnosis.

The *lymphoid cells*, which are so abundant in the young growth, are usually of the small, ordinary type. They are quite uniform in size and shape. No karyokinetic figures were ever observed in such cells. Lymphoid cells of a larger type are occasionally seen. We consider that the lymphoid cells arise from proliferation of the mother cells of the lymph nodes, and presumably also from the endothelial cells of the reticulum, which are analogous. The great increase in the number of lymphoid cells in the early stages of the disease might explain, on a mechanical basis, the occasional relative increase in the number of these cells in the blood. Such a phenomenon could not be constant, for as the fibrous tissue increases in the glands, as the disease progresses, the number of the lymphoid cells is diminished.

Plasma cells, both of the large and small variety, occur in some of the specimens in great number, lying among the lymphoid cells in the stroma. Pappenheim,[46] in a recent article on the origin of plasma cells comes to the conclusion that plasma cells and lymphocytes are "isomorphic and isochromatic," co-ordinate forms of separate origin and separate destiny. He considers, that plasma cells are undifferentiated forms of the spindle cells of the fixed tissue, and may form spindle cells under certain circumstances. We must derive both plasma cells and lymphocytes from the same tissue ultimately, and in our specimens it would seem that they arose from the proliferation of a similar cell type. It seemed evident also from our specimen that plasma cells may be transformed into connective-tissue.

Eosinophiles were present in great numbers in all but two of the cases. They appear in the tissue spaces in all parts of the gland except the germinal centres of the follicles. Practically no eosinophiles are found here, if these centres are well preserved. They often occur in greatest numbers about the blood-vessels. Very few are seen in the lumen of these vessels. The capsule and connective-tissue bands rarely contain them. They seem to appear in greatest numbers in the periphery of the gland.

In morphology they are identical with the eosinophiles of the blood. The protoplasm is full of coarse acidophilic granules. The nucleus consists of one or more spherules, taking ordinarily a deep homogeneous stain. In polychrome methylene blue, the nucleus stains a pale robin's egg blue, in marked contrast to the dark blue of the other nuclei. A single nucleolus may be seen. Mitotic figures were never observed in such cells, nor were any cells ever seen in the stroma showing evidence of beginning granulation. In the absence of any increase of these cells in the blood, and of evidence of their origin in the gland itself, we must agree with Goldmann[47] in attributing their presence to some chemotactic substance in the proliferating tissue. They are evidently normal eosinophilic cells of the blood, attracted to the lymph glands by some pathological product.

Eosinophiles are not normally present in lymph glands in any

[46] Virchow's Archiv, 1901, Bd. clxv, p. 365; Bd. clvi, p. 424.
[47] Centralbl. f. allg. Path., 1892, vol. iii, p. 665.

great number. Goldmann and Kanter[48] were the first to draw attention to the eosinophilia in lymph glands in Hodgkin's disease. Since then Dietrich[49] and Fischer[50] have emphasized this as a diagnostic point. All the observations tend to establish the fact, that an increase in the number of eosinophiles is not found in tuberculous adenitis or in sarcoma. Kanter found eosinophiles numerous in the glands of two cases, which were possibly tuberculous; in ten other cases of tuberculosis, the eosinophiles were not in excess. The case Fischer cites, in which an eosinophilia was found in the glands, but tubercle bacilli were demonstrated by animal inoculation, does not prove that Hodgkin's disease was not also present, as he at first thought. No microscopic description of the growth was given. We cannot claim that the increase is invariably found in Hodgkin's disease. The number of eosinophiles varies greatly from gland to gland and in different parts of the same gland. We believe that it is a prominent feature of the growth in three-fourths of the cases. When we understand the nature of the attraction, which causes this transmigration from the blood, we may be able to explain this variability.

Large cells, showing a very hyaline protoplasm, and numerous small oval nuclei, arranged peripherally, are seen in some specimens. These cells are often full of vacuoles. The origin of such cells in coalescence of the stroma cells, was plainly demonstrated in one section, and doubtless they all have a similar origin. They look like typical Langhans' giant cells. Ribbert[51] described the formation of such cells from the fusion of the connective-tissue cells of the reticulum in experimental inflammation of the lymph glands.

"*Kugelzellen*," such as are described by Goldmann and others, were abundant in some specimens. No especial relation to the germinal centres could be seen. Such cells did not contain pigment, as Flemming describes. Free globules corresponding to Flemming's "tingible Körpern," or the Russell fuchsin bodies, are occasionally found in large numbers. The balls in the "Kugelzellen" are apparently of similar nature.

[48] Centralbl. f. allg. Path., 1894, vol. v, p. 299.
[49] Loc. cit.
[50] Loc. cit.
[51] Ziegler's Beiträge, 1899, Bd. vi, p. 187.

Endothelial phagocytic cells and cells containing yellowish pigment granules are often seen. Practically no "red-blood-corpuscles-carrying cells" appeared.

Cells such as Hoyer[52] described as *degenerating cells* were observed. These cells, about the size of plasma cells, are characterized by a very deeply-staining protoplasm and a small dense nucleus. A few cells full of granules taking a deep gentian violet stain were seen. Flemming noted similar cells in the normal gland and suggested that they were also degenerations.

Typical "Mastzellen" were seen in a few specimens.

The *metastatic nodules* consist of exactly the same cellular structure as the glandular growth. The first appearance of these lymphomatous areas is seen in the proliferation of connective tissue cells, and lymphocytes forming a small focus anywhere in the tissue of the organ. As this increases in size by proliferation, the different cells previously described appear. As the nodules expand the tissue of the organ is pushed aside, and flattens out to form an apparent capsule. Several of these nodules may coalesce and form large irregular masses. A large lymphomatous area may invade a blood-vessel in its growth. Such a picture may be one explanation of the sudden changes in the contents of the blood occasionally recorded in this disease. The increase in connective tissue and the gradual fibrous transformation occurs as in the glandular tumors.

Miliary tubercles, large areas of caseation and tubercle bacilli were found in the lymphomatous areas and organs of one of our cases. There was little difficulty in distinguishing the two processes, and there was no reason why we should consider that the tuberculosis held any other relationship to the lymphomatous growth than that of a secondary infection. The pathological changes we have described above are utterly unlike any tuberculous process with which we are familiar. In the other seven cases we found neither tubercle formation nor tubercle bacilli. No amyloid was apparent in any of our specimens. Practically no other micro-organisms were demonstrated by any of the staining methods.

[52] Archiv. f. mikr. Anat., 1889, Bd. xxxiv, p. 204.

On the whole, this pathological picture suggests strongly a chronic inflammatory process. There is no reason to believe it is of the nature of a malignant neoplasm.

Ribbert, in his work on regeneration and inflammatory changes in lymph glands, gives a very analogous description of the reaction of the gland to injection of staphylococci. The same proliferation of endothelial and reticular cells was observed. Giant cells were also formed, although not in such great numbers or of such size, as in our specimens. The fibrosis is, of course, a later stage than any he observed. We have examined glands, the seat of a chronic infection of known origin, and observed somewhat similar changes.

No such picture is shown in tuberculosis, lymphatic leukæmia, or true sarcoma. We have never observed an eosinophilia in such tissue.

The clinical histories and the macroscopical examinations of these eight cases show a typical Hodgkin's disease. Microscopically, they present a peculiar histological picture, somewhat similar to a chronic inflammatory condition. In the literature, we usually find that Hodgkin's disease is a "simple hyperplasia of the lymph glands" or "hyperplasia as in lymphatic leukæmia." From the earliest time we find, in addition to this sweeping generalization, special descriptions of the cell types found in the specimens. Virchow speaks quite clearly of multinuclear cells and giant cells in addition to lymphoid cells, and of the coarse and fine connective-tissue stroma.

Ricker, Crowder, Ferrari and Commotti, and Sternberg, have described more fully the appearance of proliferation of the endothelial cells of the sinuses and the formation of giant cells, with the destruction of the normal glandular structure. They considered that these cases were tuberculosis and not real Hodgkin's disease. If we accepted their conclusion, we should have to consider the real disease a rare, if not unknown, process.

Kanter, Goldmann, Dietrich and Fischer have given accurate descriptions of the proliferation of endothelium, the formation of giant cells, the fibrous increase and the presence of great numbers of eosinophiles. Fortunately, they were convinced that they were dealing with Hodgkin's disease.

We believe, then, from the descriptions in the literature and

the findings in eight cases examined, that Hodgkin's disease has a peculiar and typical histological picture, consisting of proliferations of the endothelial and reticular cells, formation of lymphoid cells, and characteristic giant cells, and a gradual increase of connective tissue, resulting in fibrosis and, in most of the specimens, in the presence of great numbers of eosinophiles.

CONCLUSIONS:

1. We should limit the term Hodgkin's disease to designate a clinical and pathological entity, the main features of which are painless progressive glandular enlargements, usually starting in the cervical region, without the blood changes of leukæmia.

2. The growth presents a specific histological picture, not a simple hyperplasia, but changes suggesting a chronic inflammatory process.

3. The microscopical examination is sufficient for the diagnosis. Animal inoculation may confirm the decision by its negative results.

4. Eosinophiles are usually present in great numbers in such growths, but not invariably. Their presence strengthens the diagnosis.

5. The pathological agent is as yet undiscovered. Tuberculosis has no direct relation to the subject.

CLINICAL HISTORIES.

CASE I.—H. M. R. White boy, age 9 years.

Admitted to the surgical wards, The Johns Hopkins Hospital, November 21st, 1898.

Complained of swollen glands of the neck.

Family History.—Negative, no tuberculosis in family.

Personal History.—Scarlet fever and whooping cough only diseases. Not subject to colds or coughs, feels well and plays as other children.

Present Illness.—The glands on the left side of the neck began to enlarge two years ago, after recovering from whooping cough at 6 years of age, and have steadily increased in size. No subjective symptoms noted, no fever or dyspnœa. No pain noted in tumor mass or evidence of suppuration.

Physical Examination on Admission.—Patient rather slightly built, fairly well nourished boy. Lips and mucous membranes of good color. Slight general glandulär enlargement. Lungs negative on auscultation and percussion. Heart: slight rough systolic murmur heard over præcordium and transmitted to the axilla, no enlargement of the heart.

On the left side of the neck is a tumor mass, confined mainly to the posterior triangle and extending into the superior carotid triangle and the posterior part of the sub-maxillary triangle. The mass lies chiefly posterior and internal to the sterno-mastoid muscle, and extends from the mastoid process to the attachment of the trapezius to the clavicle. The various nodules, that make up the surface, vary in size from that of a chestnut to a hen's egg and are freely movable. The tumor is not adherent to the skin and not closely bound to the underlying tissues. Consistency is firm, elastic without fluctuation or areas of softening. The glands on right side of neck are not enlarged.

Thyroid gland is apparently slightly enlarged on the right side. Liver and spleen not palpable.

Abdominal examination negative.

Blood Examination.—

Hæmaglobin	63%
Red blood corpuscles	4,124,000
Leucocytes	12,500

Differential Count.—500 leucocytes.

1. Polymorphonuclears	50%
2. Small mononuclears	36.8%
3. Large mononuclears	3.4%
4. Transitionals	5.4%
5. Eosinophiles	4.4%

November 23rd.—.002 grms. tuberculin injected without reaction or subjective symptoms.

November 28th.—Neck measured in erect position 31 cm. at upper level of thyroid, and 29.5 cm. midway between tip of thyroid and suprasternal notch. Axillæ found to contain a few small pea-sized glands and at each apex a large nodule the size of a hickory nut.

December 7th.—Leucocytes, 8800.

Differential Count.—

1. Polymorphonuclears	56.7%
2. Small mononuclears	29.2%
3. Large mononuclears	9.2%
4. Transitionals	2.9%
5. Eosinophiles	2.9%

December 12th.—Small gland (3 x 4 cm.) removed from mass on left side of neck by Dr. Mitchell. On section the gland was opaque, yellowish and less translucent than normal. No large areas of necrosis or ecchymoses visible. Microscopical description not recorded. Wound healed per primum.

Patient was given Fowler's solution m. V t. i. d. during stay in hospital. Practically no change in condition of glands noticed.

Temperature varied from 97°-104°, and pulse from 60-115 a minute; both pulse and temperature were more regular and more normal during the last week in the hospital.

Body weight 55 pounds.

December 22nd, 1898.—Discharged.

Diagnosis.—Hodgkin's disease.

Readmitted December 7th, 1899.—Since leaving hospital has felt well and has been at school.

Physical Examination.—Practically unchanged. No dulness noted on percussion over sternum. Circumference of neck at most prominent point of thyroid cartilage 31.5 cm.

December 10th.—Blood count:

Red blood corpuscles	3,872,200
Leucocytes	6,200
Hæmaglobin	51%

Differential Count.—596 leucocytes counted.

1. Polymorphonuclears	74.6%
2. Small mononuclears	22.4%
3. Large mononuclears	3.2%
4. Transitionals	.7%
5. Eosinophiles	.05%

Temperature varied from 98°-101°, and pulse 80-110 while in hospital. Weight 54 pounds.

December 10th.—Discharged; was given Fowler's solution to take at home.

Readmitted February 5th, 1900.—Has felt well and has gone to school since discharged.

February 6th, 1900.—Blood count:

Red blood corpuscles	2,670,000
Leucocytes	10,000
Hæmaglobin	55%

Differential count made apparently showed no lymphocytosis.

Weight 56 pounds. No especial change in temperature or pulse.

February 10th, 1900.—Discharged; untreated and unimproved.

Diagnosis.—Hodgkin's disease.

After leaving the hospital the boy continued in about the same condition until the summer of 1900. He seemed strong and played out of doors as usual. During the summer he became gradually weaker and thinner until by the time of cold weather he was helpless. During the winter a troublesome cough commenced, and he was subject to fever. He complained a great deal of pain in the stomach. During the last month he had diarrhœa. He was greatly emaciated. Oedema of the extremities and ascites occurred at the last. He died January 10th, 1901. He was a patient of Dr. Watson.

Autopsy.—The autopsy was made three hours after death by Dr. MacCallum.

Anatomical Diagnosis.—Hodgkin's disease, with enlargement of cervical, mediastinal and abdominal lymph glands. Lymphomatous masses in liver and spleen. Tuberculous ulcers in larynx and intestines. Miliary tuberculosis of spleen, liver, kidneys and lungs.

Body of a somewhat emaciated boy; feet and legs markedly œdematous; genitalia not œdematous. Abdomen distended; marked diastasis of recti muscles and protrusion of intervening abdominal wall.

On left side of neck bulging below the ear, and extending to level

of clavicle is a large nodular mass, quite firm to the touch and not very closely adherent to the skin.

Abdominal Cavity.—Contains perhaps 800 cc. of clear yellow fluid.

Thorax.—The left pleural cavity contains several hundred cc. of clear yellow fluid. Right pleural cavity is dry.

The serous surfaces of pericardial cavity are smooth and glistening, and the cavity contains about 60 cc. of clear yellow fluid.

Heart.—Valves are delicate. Endocardium everywhere smooth. Heart muscle somewhat cloudy. The pleuro-pericardial membrane contains numerous translucent nodular thickenings.

On removal of the left lung the pleural surface over the dorsal portion of the ribs is found to show translucent thickening. The anterior mediastinum contains large firm nodules, which are adherent to the sternum. In the region of the left clavicle is a mass measuring 5 cm. in diameter, and above, lying below the left ear, is a lobulated mass which has a diameter of 8 cm. and a length perhaps of 12 cm. These glands are not closely matted together but are united by loose connective tissue.

At the hilum of each lung are large, firm, greyish, somewhat translucent lymph glands.

Left Lung.—Left pleura everywhere glistening. Numerous translucent grayish nodules the size of a pinhead, also a few larger, more opaque nodules, reaching a diameter of 1 cm., project from the surface of the lung. The pleura over these nodules is somewhat roughened. On section these areas correspond with opaque, yellow nodules sharply marked off from the surrounding lung substance. Three or four such nodules occur in the left lower lobe of the lung. The vessels at the base of lung are clear. Upper portion of the lung is somewhat insufflated, the lower anterior portion is, however, atelectatic. The lung substance is studded throughout with very numerous greyish translucent nodules of about pinhead size.

Right Lung.—The glands at the hilum are much enlarged and have a greyish color with opaque areas. The pleura over lower lobe is œdematous and has lost its gloss. On section the lung substance in lower lobe contains numerous nodules similar to nodules mentioned in left lung. Scattered areas throughout the cut surface have a gelatinous appearance; they project slightly above the surface and are darker in color than the surrounding lung. The cut surface is fairly smooth. Firm, somewhat opaque, yellowish nodules 1 cm. in diameter are also imbedded in the substance of the lung, particularly in lower and middle lobes. The upper lobe contains air for the most part; it is also richly studded with miliary and conglomerate tubercle-like nodules. Bronchi in both lungs contain a small amount of mucoid material.

Trachea.—At a point in the left main bronchus, 1 cm. below the bifurcation, the bronchial wall lies in close apposition to one of the enlarged glands of the trachea, and at this point the bronchial wall shows an ulceration about 1 cm. in diameter with ragged hæmorrhagic edges, the base of which is formed by necrotic substance of the gland.

Larynx.—In the inter-thyroid angle in larynx there is an ulceration of the mucosa about 1 cm. in diameter, just below epiglottis. The

margins are slightly elevated and nodular, and in the central portion there are small translucent nodules projecting above the surface. No especial congestion of the mucosa above the ulcer.

The *lymphatic glands* along the spinal column and in the pelvis, at the inguinal ring, in fact, wherever examined, are markedly enlarged and firm. The larger show on section an opaque necrotic area in their interior.

Cervical Glands.—On section these glands have a greyish translucent appearance but almost uniformly show large irregular areas of opaque yellow color.

Diaphragm is thickened here and there by means of enlarged glands which on section have a similar appearance.

Liver.—The liver is large, measuring 23 x 18 x 8 cm. Surface is studded with yellowish semi-translucent nodules varying in size from small nodules, scarcely visible to the naked eye, to large conglomerated masses 8-10 cm. in diameter. In many instances the surface shows long branching bands of yellow translucent material, apparently following the lymphatics in the walls of the superficial vessels. The projecting nodules are surrounded by a somewhat congested area. The lymph glands at the porta of the liver are also enlarged. On section the substance of the liver is found to be filled with such nodules. They are frequently collected in the walls of the vessels, forming somewhat nodular whitish thickening of the wall.

Many nodules are discrete and resemble on section the cut surface of the large glands. In other areas the lobular structure of the liver is apparently not destroyed but the opaque material is so deposited in them that they give rise to a coarse lobulation somewhat resembling that of a cirrhotic liver. The liver substance when not involved shows no especial abnormality.

Gall Bladder.—Much distended with pale bile; the distention being due to compression of the bile ducts by masses of glands.

Intestines.—Colon apparently normal except just at the ileocœcal valve, where the margin of the valve on the colon side and the colon wall for a distance of 5 mm. has lost the mucosa. This ulceration is crescentic in form and extends almost over the whole circumference of the ileocœcal ring. Its edges are somewhat elevated and have a gnawed appearance. The mucosa at the edge of the ulcer shows a few hæmorrhages. The base of the ulcer is of a rather granular appearance. The serous surface of the gut is smooth. On the lower portion of the ileum there are a few small ulcers of a similar appearance.

These ulcers show definite translucent nodules in their base. They occur as high as a point 25 cm. from ileocœcal valve. The remaining intestine is apparently normal.

Stomach and duodenum show no abnormalities.

Œsophagus.—At the level of the cricoid cartilage are a few small erosions and similar eroded areas reaching 2 cm. in diameter extend above the cardiac orifice.

Spleen.—Much enlarged. The surface is irregular from the presence of projecting nodules; one large whitish nodule about 2.5 cm. in diameter is situated at the hilum. On section the elements of the spleen are readily seen. Numerous firm, opaque, yellow nodules, aver-

aging 5 mm. in diameter, are scattered through the substance. They are sharply outlined by a greyish translucent material with small hæmorrhages. Very numerous small translucent nodules about pinhead size are scattered throughout the spleen.

Kidneys.—Left measures 10 x 5.5 x 4.5 cm. Capsule strips readily. Stellate veins are injected. Scattered over the surface are translucent nodules 2-3 mm. in diameter. Cortex averages 5 mm. in thickness. Striations plainly visible. Glomeruli readily seen. Kidney slightly pale. Right kidney similar in general appearance.

Enlarged glands in the neighborhood of pancreas and behind stomach form a mass about 10 cm. in diameter, closely adherent to stomach and pancreas.

Pancreas.—Quite firm and sharply outlined from immediately adjacent glands. On section, one rather opaque yellowish nodule is seen in the substance.

The *fresh autopsy material* was preserved in Zenker's fluid, alcohol, Orth's and Flemming's fluids.

Smears were made directly from the various lymphatic glands, the liver, lungs and spleen. Numerous typical tubercle bacilli were demonstrated in the smears from the enlarged cervical and bronchial glands, and from the lung. A few bacilli were found in the smears from the liver, but none could be found in those from the spleen.

A *rabbit inoculated* subcutaneously with a small piece from the enlarged cervical glands died thirty-one days afterwards.

At the autopsy two large caseous masses, containing numerous tubercle bacilli, were found at the point of inoculation.

On microscopical section these areas were found to consist of the degenerated particle of gland originally introduced, infiltrated with leucocytes, and partially encapsulated by new-formed fibrous tissue in which leucocytes and numerous tubercle bacilli could be seen. No giant cells of the Langhans' type were visible. The lymphatic vessels, in the neighborhood of this mass, were injected and several large swollen lymph glands were adjacent. The left adrenal showed small, elevated, whitish nodules, the size of a pinhead, over the lower pole. On section the gland itself was apparently normal with the exception of small nodules of lymphoid tissue, which were found about the periphery of the organ. Areas of degeneration, containing fragmenting nuclei and leucocytes, were found in these areas, but there was no typical caseation or giant cells. No tubercle bacilli were demonstrated.

The other internal organs and the serous membranes were apparently normal. The enlarged lymph glands, adjacent to the field of inoculation, showed on microscopic examination a few miliary tubercles.

Microscopical Examination.—The enlarged cervical glands, undoubtedly the original focus of the disease, could not be removed, owing to the objections of the family.

The *large glands* elsewhere in the body showed practically a uniform condition. The most marked feature is the great increase in connective tissue and the areas of hyaline degeneration and necrosis. The capsule shows moderate thickening, and in one instance large collections of lymphoid cells were found lying between the connective-tissue bands of the capsule.

The blood-vessels are very abundant, without endarterial changes, and are usually full of blood. The lymph sinuses are numerous and dilated. The increase in fibrous tissue, which is the chief distinction of these glands, seems to start from about the vessels, in periarterial thickening, and from the connective tissue of the lymph spaces. The gland substance is broken up by these coarse bands of connective tissue into islands of cellular tissue. The coarse fibrous strands often show hyaline degeneration. The increase in the connective tissue is also well marked in the general increase in the fine reticular framework of the gland.

Toward the centre, and in patches in the periphery, are found large areas taking a very deep stain in the acid dyes, and showing almost complete loss of cellular outline. Such degenerated portions are usually surrounded by tissue very poor in cells, consisting of the connective-tissue framework which has undergone hyaline degeneration. There seem to be here regular steps in the process of degeneration, probably due to anæmic necrosis; first the disappearance of the cellular elements, leaving the more resistant fibrous tissue stroma, then the gradual hyaline transformation of the cells, with the final changes into necrotic masses showing no resemblance to the living tissue.

In some of the glands examined these degenerated areas exceeded in amount the rest of the gland. Foci of fragmented nuclei and degenerating cells are often seen in these areas, and occasionally small areas of necrosis in otherwise apparently normal tissue. Tubercle bacilli are found in some of the glands in the apparently normal tumor tissue, as well as in these areas of necrosis. In other specimens no tubercle bacilli are found anywhere in the gland. No structure suggesting tubercle formation or Langhans' giant cells was observed.

In one gland numerous thrombosed vessels were found. The walls of these vessels are infiltrated, partly necrosed and the thrombi show evidence of degeneration. Numerous tubercle bacilli were demonstrated in these thrombi, but none were found anywhere else in the gland. This is suggestive, as the probable mode of invasion of the tubercular process, which here is undoubtedly secondary to the lymphomatous enlargement.

The cellular portions of the glands, which are cut into islands by the fibrous bands and are in greater abundance toward the periphery, show a typical and uniform structure. No sign of the original glandular anatomy is left. The reticular framework is much increased and covered by large epithelioid cells which form a mesh work in which lie numerous lymphoid cells, plasma cells and giant cells. The large lymphoid cells and plasma cells outnumber the smaller lymphocytes. Mitoses in cells of the large type are frequently observed. The farge uninuclear and multinuclear giant cells are very abundant and give evidence in their structure, in the cell processes and nuclear formation, of relation to the abundant epithelioid cells of the stroma.

Eosinophilic cells are quite numerous, and seem to be found in greater numbers about small vessels. No eosinophiles were found in the capsular tissue. A few "Mastzellen" were demonstrated by the polychrome methylene blue stain. A few cells containing "kugel" were observed, but in no great numbers. In one specimen stained by the

Weigert fibrin stain, one cell full of small even-sized granules, staining deeply in gentian violet, was observed. This cell had no definite nucleus. Similar cells have been described by Flemming in the normal lymph gland.

No micro-organisms, with the exception of the tubercle bacilli, were demonstrated. There was no amyloid degeneration or fibrin observed.

A *small abdominal* gland, less than 0.5 cm. in diameter, shows a very interesting and typical picture of the early changes in the disease. The capsule shows neither infiltration nor thickening. The blood-vessels are numerous and full of blood. The most striking feature is the number and the dilatation of the lymph sinuses. The connective tissue, on close study, is found considerably thickened. It seems to be increased, especially about the sinuses and to form rather firm bands, breaking up the structure into irregular islands of more densely cellular tissue. Connective-tissue bands radiate through the gland in every direction. The general structure of a lymph gland has been lost; there are, however, several lymph nodes still preserved towards the periphery of the gland. These nodes consist of masses of lymphoid cells and plasma cells, with numerous large epithelioid cells forming a mesh in which these other cells lie. A few giant cells are also seen here. Eosinophilic cells are also numerous, especially toward the periphery of such nodes.

The tissue is extremely cellular. The dilated sinuses are lined and intersected with large, irregular, epithelioid connective-tissue cells, showing branching protoplasmic processes and large oval vesicular nuclei. These cells are evidently proliferations from the cells covering the reticulum and form a mesh work by their anastomosing processes in which lie the free cells of the tissue. Such cells as these also lie free in the tissue spaces, and variation from them to the large uninuclear giant cells are easily found.

The giant cells, which are numerous, vary in size and appearance. We find large cells many times the size of a small lymphocyte with a single, deeply staining nucleus, filling out most of the cell. The chromatin network and nucleoli are always a marked feature, resembling in detail the nuclear framework of the epithelioid cells. Cells with two or more nuclei are common, while many cells with four to eight nuclei are seen. The nucleus is the chief feature, always relatively large for the size of the cells, often oval and bizarre shaped, having a heavy chromatin granulation and one or more large nucleoli. These nucleoli always stain in a contrasting color to the nucleus in the double stains.

The proportion of lymphoid cells in the specimen is relatively large, and plasma cells are found in almost equal numbers. The lymphoid cells are mainly of the large type. The plasma cells vary in size and in number of nuclei. Mitotic figures were frequently seen in the large cells.

In the polychrome methylene blue preparations quite numerous "Mastzellen" are found lying among the plasma cells.

Eosinophilic cells are very abundant, making up in places as many as one-third of all the cells in the field. They do not seem to bear any relation to the vessels, and occur, as said, around the lymph nodes.

The *nodules of the pericardium* are found to consist of a similar structure.

Cellular portions consisting of exactly the same elements as described above, are separated by connective-tissue bands. Small areas of necrosis with fragmenting nuclei are abundant. No tubercle bacilli or Langhans' giant cells were seen.

Several peculiar large cells, looking like endothelial cells, were found in the tissue spaces. These cells, which stained very deeply, were filled with coarse, dark, irregularly staining bodies. This was more suggestive of nuclear fragmentation than of "kugel."

The *Sections of the Liver.*—Show large lymphoma nodules, and small areas of lymphoid tissue with tubercle formation.

The capsule appears normal, without infiltration or thickening. The capillary spaces between the liver cells are dilated, filled with blood, lymphocytes and epithelioid connective-tissue cells. Large endothelial cells, vacuolated or filled with dark brown pigment granules and pigmented leucocytes also appear in these spaces. Occasionally a large uni or multinuclear giant cell can be found between the liver cells, and such cells frequently contain pigment granules.

The liver cells between the capillaries are compressed, but the outline of the lobule is still well preserved. The staining reaction of the cells varies greatly, otherwise the liver elements appear normal.

The earliest lymphoma formation, with the exception of isolated giant cells, is seen in small groups of epithelioid connective tissue and lymphoid cells. These collections appear anywhere in the lobule or at the portal space. The process cannot be said to start in any especial part, although there is a uniform connective tissue increase about the vessels. In the smallest lymphoid nodules seen, we find quite circumscribed masses, with tangentially flattened liver cells surrounding them. As such nodules enlarge, they may meet and coalesce at some point, and form large irregularly-shaped masses, containing isolated groups of liver cells in their growth. There is no definite capsule to these areas, the edge of the nodule may be quite sharply cut but frequently is irregular from infiltration of the liver tissue by the epithelioid cells. In the large macroscopic lymphomatous areas, an isolated liver cell or a bile duct may be left as a clue to the manner in which they have arisen.

The small lymphomata consist of large epithelioid cells, forming a network, in which lie large and small lymphoid cells and leucocytes. A few eosinophiles, and occasionally one of the large giant cells, showing processes like connective-tissue cells, are seen. In the large nodules the epithelioid cells have bigger and more vesicular nuclei, and form a wide meshed structure. The reticular framework of such an area can be demonstrated by the Mallory connective-tissue stain. Eosinophilic cells are in great numbers, equalling in places half the cells present. They do not appear in the liver tissue, and have no especial relation to vessels. The typical giant cells are also more abundant in the large nodules. No "Kugelzellen" and but few plasma cells are present.

There are no areas of degeneration or necrosis, but the epithelioid connective-tissue cells in places appear almost without the free-cell elements, and show a diminution in the number of their nuclei—a

process suggesting the anæmic necrosis observed in the glands. The blood supply to the large areas appears very slight, very few vessels are seen in the nodules. In one section a large blood-vessel was found with muscular walls for two-thirds of its circumference still intact, but the rest of the coat was infiltrated with connective-tissue and lymphoid cells. The lumen of the vessel was almost filled with a typical lymphoma nodule, which appeared to have grown in at one side of the vessel.

Several small areas of epithelioid and lymphoid cells are found, especially near the large vessels, and containing usually one or more typical Langhans' giant cells. A few tubercle bacilli can be made out in such foci, but none were found elsewhere in the sections. No amyloid degeneration was found in the liver.

Sections of the Spleen.—Show large and small areas of lymphoid tissue, corresponding in every particular to the glandular structure. The splenic pulp shows considerable increase in the connective tissue. There is a tendency to tangential flattening of the tissue about the larger lymphoid nodules. The capsule is apparently normal. Several Malpighian bodies are still to be made out. The capillaries of the pulp are full of blood and often contain large endothelial cells which are phagocytic. The vessels are numerous and show peri-arterial thickening. The lymphoid nodules are more abundant as we pass inward from the capsule. The centres of the large nodules show patches of hyaline degeneration. Large areas of cellular necrosis, with fragmenting nuclei are also found.

Numerous typical Langhans' giant cells, usually surrounded by a few epithelioid cells, are found here and there in the splenic pulp, usually without any relation to the lymphoma masses. Tubercle bacilli are easily demonstrated in such places, but nowhere else in the section.

Considerable coarse, golden-brown pigment was observed in the endothelial cells of the vessels, and in some of the leucocytes.

In the lymphoma masses the eosinophiles were especially abundant, while a few were found in the connective tissue of the pulp. It was noted that none were to be seen in the Malpighian bodies, nor in the blood-vessels, nor especially grouped about the blood-vessels.

The Lungs.—The alveoli and tissue surrounding the bronchi show infiltration with polymorphonuclear leucocytes and lymphoid cells. The lumen of the bronchi and alveoli are full of desquamated epithelial cells and leucocytes. Numerous tubercle bacilli are found in such areas. No giant cells or areas of caseation were seen. Nothing suggesting lymphomatous growth is observed. A few eosinophiles were seen in the vessels about the bronchi.

The Kidneys.—Were apparently normal except for a few typical miliary tubercles found in the cortex. Tubercle bacilli were easily demonstrated in such foci.

The Intestinal Ulcer showed an infiltration of the mucosa and submucosa with lymphoid and plasma cells, and leucocytes. Numerous giant cells and tubercle bacilli were demonstrated. No lymphomatous tissue was observed.

Case II.—J. R., female. White. Age 55. Admitted to The Johns Hopkins Hospital, service of Dr. Osler, May 28th, 1899.

Family History.—Unimportant. One sister died of consumption.

Personal History.—Patient had had the diseases of childhood, typhoid fever, pneumonia and epilepsy when a child. She had been a healthy, strong woman, usual weight 250 pounds. Had never been subject to cough, dyspnœa or night sweats. Swelling of the feet for the last ten years. No digestive symptoms. Habits excellent; non-alcoholic. Married. One child; no miscarriages. Menopause at 44.

Present Illness.—Dates from the appearance of a small flat nodule in the episternal notch, apparently over four years ago. The mass gradually increased, reaching the size of a dollar in one year. About three years before admission separate nodules appeared on either side of the neck above the shoulder and below the chin. Growth was gradual until a year ago, when increase was rapid, mass becoming in this time four times the original size. Became feverish about three years ago. Has had numerous shaking chills at irregular intervals, followed by fever. No sweating except about the face. The chills and fever were worse during the past year. For the past year she has been short of breath. For the past six months she has had a great deal of sharp pain in the chest and under the shoulder. Her feet have swollen previous to the present illness, but the œdema has been worse for the past year. For three weeks there has been marked œdema of the hands and forearms, especially on left side. There has been no headache, giddiness or tinitus aurium. Her hearing is somewhat impaired. Considerable greenish muco-purulent expectoration for past three weeks of a sickening odor. Appetite poor. Diarrhœa since onset of illness. Gets up three to four times at night to pass water. For past six weeks swallowing has been difficult; can only take liquid nourishment.

Physical Examination.—Large framed, well nourished woman. Face puffy. Pupils normal. Tonsils not enlarged. Lips and mucous membranes fair color. Enormous enlargement of the cervical glands in the anterior and posterior triangles, especially on the left side. The chin is practically obliterated by the enlargement of the glands in the median line; the episternal notch and clavicular fossæ are entirely obliterated. The thyroid is apparently also involved. The glands invade the supraspinous fossa posteriorly. The neck measures 50.5 cm. in circumference. The glands are fairly well matted together, firm in consistency, no fluctuation. The skin is freely movable over them.

In the right axilla the glands are enlarged, but freely movable and not matted together. In the left axilla the glands are also considerably enlarged but not as much so as on right side. The inguinal glands are but little involved, the largest gland being no larger than a lima bean. Marked œdema of left hand and forearm; slight œdema of right arm. Enormous œdema of feet and legs.

Thorax is well formed. Percussion is dull over manubrium and in the interscapular region. Clear over front and axillæ. Breath sounds markedly enfeebled throughout; of a tubular character over manubrium. No adventitious sounds.

Heart.—Negative. Pulse at left wrist much smaller than on right.

Liver.—Relative hepatic dullness begins over middle of fifth rib in

parasternal line and extends just to costal margin. The lower border of the liver can be felt 8 cm. below costal margin in parasternal line. The border is irregular, somewhat nodular and very sensitive to pressure.

Abdomen is markedly pendulous. Large umbilical hernia.

Spleen not definitely palpable.

Retro-peritoneal glands apparently not enlarged.

Blood examination, May 29th:

Red blood corpuscles	4,784,000
Leucocytes	10,500
Hæmaglobin	65%

Differential count:

Polymorphonuclears	84%
Small mononuclears	14%
Large mononuclears	0.8%
Transitionals	0.6%
Eosinophiles	0.4%

During stay in hospital patient suffered with extreme diarrhœa; the stools contained neither blood nor mucus.

Dullness developed at the base of both lungs with numerous moist râles. Respiration was very noisy, stertorous when asleep. Considerable muco-serous expectoration. Difficulty in swallowing, though there is no definite pain. Takes only liquids. Slightly irregular elevated temperature, highest point reached was 101.5°. Œdema somewhat decreased.

Complained of general discomfort but of no definite pain. Heart remained negative. Became gradually weaker and respiration more labored.

Found dead in bed June 4th—10 P. M.

Autopsy, June 5th, 10 A. M.

Anatomical Diagnosis.—Hodgkin's disease; tumor masses in cervical and axillary regions. Nodules in anterior and posterior mediastinum, compressing trachea, œsophagus, etc., involvement of retro-peritoneal and pelvic glands. Nodules in periportal space, liver and spleen. Cirrhosis of the liver. Chronic diffuse nephritis. Nodular colitis, circumscribed lipoma of colon.

Large stout woman, 164 cm. long. Marked œdema of legs. Inguinal glands palpable, axillary glands enlarged, cervical glands form large tumor mass on either side of neck, extending across mid-line. Umbilical hernia.

Lungs insufflated, meet in mid-line. Anterior mediastinal glands are large and firm.

Left pleural cavity contains 200-300 cc. of fluid. Posterior portion of lower left lung atelectactic, dark purple in color, airless, containing much fluid. Also area of atelectasis in lower right lobe.

Right bronchial glands enlarged, measure 3.5 x 1.5 cm., firm, translucent and whitish. At bifurcation of bronchi, small translucent masses are to be found which evidently compress the lumen of the bronchus. Lung substance is pale, dry and air-containing. At upper and mediastinal space there is a firm nodule apparently continuous above with

masses in neck, and reaching downward 8 cm. from episternal notch to level of third rib. This might compress bronchi or possibly aorta. The glands in posterior mediastinum, just above diaphragm, and in front and at side of aorta, are enlarged and hard.

The *mass* of cervical glands removed with the mediastinum weighs 2000 grams. Tumor mass invades especially the left side of neck and encircles the left clavicle, which however is apparently free. The tumor consists of a mass of nodules matted together, varying in size from 2-9 cm. in diameter. Transversely the mass measures 29 cm., vertically, 20 cm.

The aorta is encircled at the arch by the tumor. The œsophagus is almost encircled by the tumor, and is displaced towards the left by a large mass at the level of the larynx, which apparently compresses the lumen. The trachea is embedded in the tumor, but is not markedly compressed except just below the cricoid cartilage, where it is bent at an obtuse angle toward the left. Here it is flattened laterally, and there are ulcerations on its internal surface. The brachial plexus of nerves, and also brachial vessels, are encircled by the tumor mass. On section through a large mass, the nodules are found densely bound together, and to the skin. The substance of the tumor is brownish and translucent, with irregular areas here and there of an opaque yellowish-white color. These areas are quite soft and resemble caseous material. The translucent portions have an elastic consistency and scrapings are rather glutinous. The mass of glands is apparently continuous over right shoulder.

Axillary glands on left side are enlarged and measure 7.5 x 3 cm. Series of nodules extend below the left ear in the occipital region.

Spleen.—Weighs 400 grams. Measures 16 x 10 x 7 cm. Surface is smooth. Capsule tense. Color deep blue. Near the anterior margin is a small projecting nodule about 1.5 cm. in diameter, rather paler in color and firmer in consistency than the surrounding tissue. On section the splenic pulp is apparently rather increased in amount. Trabeculæ and vessels are apparent. Malpighian bodies are in great part marked by semi-translucent whitish nodules, varying in size from 1 mm. to almost 1 cm. These have an irregular outline and are fairly sharply marked off from the surrounding tissue, they have no evident relation to the blood-vessels. The nodule projecting from surface is one of these. There are two small hæmorrhages into the spleen pulp.

Mesentery.—No large nodules in mesentery. At the cardiac orifice of the stomach, just below the diaphragm, are nodular masses extending to the head of pancreas and porta of liver, where they surround the cystic and common ducts, which however are patent. The nodules in the wall of the gall bladder measure 13 mm. in diameter.

Stomach.—Practically normal.

Small Intestines.—Are injected throughout, and in lower ileum numerous ecchymoses appear. Peyer's patches and solitary follicles not enlarged. From cæcum down, but more extensive near sigmoid flexure, are superficial irregular ulcerations of mucosa, with a few small slightly elevated nodules with ulcerated apices.

Pancreas.—Normal. *Gall Bladder.*—Normal.

Liver.—Weighs 2240 grams. The surface is somewhat roughened,

especially near the margin, and near the edge of the right lobe, where there is a depressed scar. Surface of the liver is a yellowish pink and scattered over it are numerous translucent projecting nodules. Liver is quite firm in consistence and measures 28 x 23 x 9 cm. On section the nodules are visible throughout the liver substance. The lobules are opaque pinkish yellow; they are evidently separated by a somewhat translucent new growth of connective tissue. The nodules in liver are very numerous; apparently of same nature as those described above.

Kidneys.—Weigh together 300 grams. Very freely movable. Capsule strips with difficulty; somewhat thickened. Dark in color; consistency increased. Cortex 6 mm. thick, of uniform purplish color; moist on surface. Striations and glomeruli somewhat obscured. Epithelium has an increased opacity. Apparently no nodules in kidney.

There was a mass of retro-peritoneal nodules which on section have appearance of tumor masses described above; they extend from bifurcation of aorta to the diaphragm.

Pelvic Glands.—Are also involved.

Uterus and appendages show nothing important.

Bladder and *adrenals* normal.

Bacteriological Examination.—Heart's blood: Micrococcus (unidentified). Lungs, spleen and cervical glands, sterile. Kidneys and liver, B. coli. Liver, Staph. pyog. aureus.

The tissue was preserved in alcohol and Zenker's fluid.

Microscopical Examination.—A careful examination was made from glands from different portions of the body, and as the changes varied the condition found in several specimens will be described in detail.

A medium-sized gland from the axillary region was sectioned in toto. This presented the most typical picture. The most striking feature was the increase in the number of the blood-vessels present. There were more vessels in the region of the hilum, but large and small vessels appear in great numbers everywhere. Under the high power the gland seemed made up of a network of capillaries full of blood. The walls of the vessels showed periarterial thickening, and often form centres of radiating connective-tissue bands.

In this gland there was no great increase in the number and size of the lymph sinuses. The afferent lymphatic vessels just beneath the capsule were somewhat dilated. The normal appearance of a lymph gland, with its divisions into follicles and sinuses, was completely obliterated, although a few lymph nodes were still evident. The capsule was little if any thickened. Its blood supply was rich. There was slight infiltration of the capsular tissue with lymphoid cells.

From the hilum, coarse connective tissue bands passed up into the substance of the gland, dividing it into large lobules. Coarse and fine strands radiated from these heavy bands, and passed through the gland. The increase in connective tissue was everywhere marked but in some places, especially near the hilum, a dense connective-tissue overgrowth had almost completely replaced the cellular elements.

The lymphatic channels contained numerous lymphocytes and large endothelial cells. Similar large epithelioid cells were found in the reticular spaces. These cells have large oval vesicular nuclei with a prominent nucleolus. The bulk of the tissue consisted in the mesh

work made up of connective-tissue cells, in which lay lymphoid cells, the epithelioid cells previously mentioned, and numerous giant cells. The lymphocytes were of the usual type, and of a uniform small size. The epithelioid cells were numerous, and it was in cells of this size that we frequently found mitotic figures. Large cells, several times the size of an ordinary endothelial cell, having as a rule one large nucleus filling out three-fourths of the protoplasm, were next to the lymphoid cells, the prevailing cell type. Undoubted transition from such cells to the epithelioid cells were frequently seen. The origin of the epithelioid cell is evident in the number of similar cells found in the lymph sinuses, or spaces, arising from proliferation of the endothelium. Cells having two or more large oval or irregular nuclei, with characteristically prominent nucleoli, were evidently further development of the large uninuclear cells.

No eosinophilic cells or "Kugelzellen" were observed. Few plasma cells were seen. One large lymph node near the hilum was still preserved, surrounded by large lymph sinuses. The center of this node was extremely vascular and in the reticular spaces numerous large epithelioid cells and the giant multinuclear cells were found. Quite numerous karyokinetic figures were observed here.

A section of a large inguinal gland showed a most extensive increase in the connective tissue. Almost all the glandular structure had been replaced by coarse bands of connective tissue, which were undergoing hyaline transformation. Isolated spots of cellular tissue about the vessels showed the same structure as observed in the axillary gland. Cells undergoing degeneration, fragmenting nuclei and large phagocytic giant cells were frequently seen.

Another large gland, very similar in appearance to the first one described, showed large pale-staining areas scattered through the tissue. These areas consisted of degenerating cells, and were infiltrated with polymorphonuclear leucocytes. A large vessel in the section showed an infiltration of the wall with leucocytes, and numerous degenerating cells in the lumen. Phagocytic endothelial cells, especially in the necrotic areas, were abundant. No tubercle bacilli or other micro-organisms could be demonstrated. A few cells, consisting of a very densely-staining protoplasm and a small dark oval homogeneous nucleus, were occasionally seen.

In other glands plasma cells were found in great numbers, and in one case numerous polymorphonuclear leucocytes were present without any apparent areas of necrosis.

The mesenteric gland examined showed very large areas, the centres of which consisted of cells which had undergone a hyaline transformation. The outlines of the cells were lost, only a few nuclei were left entire, but numerous portions of fragmented nuclei were seen. Around the area the tissue was very poor in cells, consisting mainly of the connective-tissue stroma, the meshes of which contained numerous red blood corpuscles. Polymorphonuclear leucocytes were not found in any great number. The entire gland showed a great increase in connective tissue and was very vascular. In this specimen and in several others very large cells with a dense homogeneous protoplasm containing numerous small oval nuclei were found.

No tubercle bacilli were demonstrated in any section examined.

In a few instances considerable amount of yellowish pigment was found between the endothelial cells of the sinuses. A large multinuclear cell full of such granules was observed.

Eosinophilic cells were rarely seen in any specimen examined. No typical "Kugelzellen" were noted.

The section of the liver showed a marked increase in connective tissue in the portal spaces, and extensive fatty degeneration of the liver cells, and the presence of lymphomatous nodules. The fatty degeneration of the liver cells seemed to affect the periphery of the lobule first, but there was often complete transformation of the entire lobule. Such areas showed only masses of fat and degenerating liver-cell nuclei with an occasional liver cell intact. The reticular structure was still preserved. The large lymphomatous masses were made up of a coarse connective-tissue framework, which passed out from the edge of the nodule into the reticular framework of the lobule and toward the neighboring portal spaces. The process in all the sections examined had gone so far that it was difficult to trace out the preceding stages. The periphery of the nodules furnished, however, evidence of the manner of growth.

There was never any capsule to the nodules, the liver cells at the periphery, if still preserved, were flattened out tangentially from pressure of the growing mass. The connective tissue of the reticulum at the edge of the nodule was filled with numerous lymphoid cells and large epithelioid cells. The nodule evidently grown by proliferation of these cells and invasion by them of the reticular spaces. As a rule there was no real liver tissue left for them to replace, as it had already undergone a fatty degeneration.

The portal spaces show considerable increase in the connective tissue, which contains numerous lymphoid cells. The structure of the lymphoma nodule is practically the same as the growth in the gland. The large multinuclear cells are very numerous. Plasma cells and eosinophiles are rarely seen. An occasional isolated liver cell may be seen in the nodule. A few large multinuclear giant cells were observed. In the large nodules mitoses are frequently seen. Cells undergoing degeneration with fragmented nuclei were observed. No areas of necrosis occurred. Nothing suggesting tuberculosis was seen. No tubercle bacilli could be found.

Sections of the spleen show large lymphomatous nodules about which there is considerable increase in connective tissue.

In the splenic pulp small vessels are frequently seen full of plasma cells and the periarterial tissues were infiltrated by such cells. In one place the endothelium of a large vessel was raised by the number of plasma cells lying beneath it and in the lymph spaces. Large epithelioid cells, evidently proliferation of the endothelium of the sinuses, were often observed in otherwise normal tissue.

Groups of epithelioid cells, lymphocytes and plasma cells often placed about a small vessel suggest the beginning of lymphomatous areas. The small lymphoma nodules consist of framework of connective tissue in which lie such cells and giant cells as described in the glands. Such foci are quite sharply marked off from the rest of the tissue by tangentially flattened out fibrous tissue. There is no definite capsule.

The large nodules are broken up by very coarse connective-tissue bands which run in every direction. They show, besides a marked connective-tissue increase, the same elements as the small nodules. Giant cells are conspicuous. Some of these large nodules consist of apparently separate masses bound together by fibrous tissue. This suggests coalescence of the smaller masses to form the larger areas.

Plasma cells are infrequently seen in the large nodules, but polymorphonuclear leucocytes are found in considerable number. Very few eosinophiles were seen. A few "Kugelzellen" were observed. In places the fibrous bands showed a tendency to hyaline degeneration. There were no areas of necrosis. Tubercle bacilli were not found. A few remains of Malpighian bodies were left but these showed no especial changes. The vessels of the spleen showed marked periarterial thickening. The capsule was apparently normal.

No lymphomatous areas were found in the other organs examined. No evidence of tuberculosis was seen in any part. There was a chronic nephritis and a chronic passive congestion of the lungs. There was slight superficial ulceration in the intestines, but not of a tuberculous nature.

Case III.—W. H. Colored boy, age 5 years; admitted to The Johns Hopkins Hospital, service of Dr. Halsted, April 27th, 1895.

Family History.—Negative. No tuberculosis.

Personal History.—No diseases of childhood except whooping cough, during the last winter.

Present Illness.—Glands of the neck have been enlarged for about two years.

Physical Examination.—Child has a bad cough, said to be the last of whooping cough. Profuse stomatitis with fœtid breath. The finger ends are clubbed.

Chest.—The left side does not expand as much as right, is dull on percussion and tubular breathing is audible on auscultation.

Spleen is palpable.

Liver is not palpable.

The glands on the left side of the neck are enlarged and occupy the submaxillary space, extending up behind the angle of the jaw and down to the clavicle and forming a mass as large as a goose's egg. The glands on the right side are enlarged in the supra-clavicular region, and under the inferior maxilla. Other glands of the body are not enlarged.

Urinary examination negative.

No blood count made. No tuberculin given.

Weight on admission 33 pounds.

Temperature varied irregularly from 96°-101°. Pulse from 100-145.

Child died May 3rd, 1895.

Autopsy by Dr. Flexner.

Anatomical Diagnosis.—Mixed cell sarcoma of lymphatic glands and spleen.

Body.—125 cm. long, emaciated, rigor mortis fairly well marked. Lividity of dependent parts. Mucous membranes very pale. Œdema of

scrotum, feet and ankles. Subcutaneous fat in small amount. Muscles pale.

Marked swelling on both sides of neck, especially on left. The swelling seems to be made up in part of individual glands varying in size from a pea to a hazel-nut; but in part the glands are massed together, forming a nodular tumor. The glands are moderately firm, nowhere fluctuating. The skin in places is adherent to the tumor mass.

Glands in axilla and groin are not enlarged.

Peritoneal Cavity.—Contains 250 cc. of clear amber fluid. Both surfaces of the peritoneum are smooth. Diaphragm reaches to the 5th space on either side.

Pericardial Cavity.—Contains 50 cc. of clear yellow fluid. Both layers of the pericardium smooth.

Heart.—Weight 90 grams. Endocardium smooth throughout. Valves appear normal. Myocardium pale and homogeneous in appearance.

Pleural Cavities.—Contain about 150 cc. each of light yellow fluid. Parietal pleura is smooth, visceral pleura is smooth except for a few greyish translucent bodies, round and about the size of a pin's head, scattered over the surface; these are most marked near the hilum of the lung. On section they are translucent and of a homogeneous grey color.

Lungs.—Right upper lobe is soft and crepitant with the exception of a small portion adjoining the middle lobe, which is firm and consolidated. On section are seen scattered here and there through the lobes translucent grey nodules about the size of miliary tubercles. The same appearance is observed in the lower lobe, which is, however, somewhat congested and from which a small amount of frothy fluid can be squeezed. The middle lobe is much more firm to the touch than the other two. On section the same translucent bodies are seen but in greater number. The lung substance is reddish-brown in color, and mottled. The bronchi in this lobe are filled with a thick sticky exudate. The upper lobe of left lung presents the same appearance as upper lobe of right. The lower left lobe is somewhat congested. The translucent nodules are seen in moderate number in both lobes. At the hilum of this lung one of the anterior mediastinal glands has grown into the lung substance, apparently breaking through the capsule and invading the lung tissues to a slight extent. The bronchi appear dliated. The mucous membrane is congested and filled with a sticky muco-purulent material.

Trachea was congested.

Spleen.—Size 14 x 6.5 x 3.5 cm. Surface of spleen is smooth except at hilum, where it is adherent to a mass of enlarged lymphatic glands. The surface feels markedly irregular; on section this is seen to be due to numerous nodules lying beneath the capsule. These nodules are diffusely scattered all through the substance of the spleen. They vary in size from 1-5 mm., for most part are round, though occasionally little tongues of spleen substance seem to penetrate into them. They are moderately firm in consistency, yellow-grey in color. The smaller ones are homogeneous and the larger ones show patchy areas, yellower than the rest of the nodule. Between these nodules the spleen substance

seems normal, the pulp dark red, the Malpighian bodies pale but easily visible and the trabeculæ well marked.

Liver.—Weight 570 grams, size 20 x 12 x 4.5 cm. Surface smooth, section rather pale with a slight yellowish tinge. One or two small translucent nodules size of pin's head in liver substance. Gall bladder contains moderate amount of clear brownish bile. Gall duct is patent.

Kidneys.—Weight 150 grams. Size 7.5 x 5 x 3.5 cm. Capsule strips off easily. Surface smooth. On section pale cortex seems thicker than usual, averaging about 6 mm. Pyramids pale, otherwise appear normal. Glomeruli pale, barely visible. Mucous membrane of pelvis smooth.

Œsophagus, Stomach and Intestines.—Appear normal except that the Peyer's patches and solitary follicles of the large intestine are somewhat swollen and more prominent than normal.

Bladder and Testicles.—Normal.

Glands—Cervical.—On right side running parallel to the sterno-mastoid is a mass of glands 12.5 x 4.5 x 2 cm. in extent; this mass is mostly composed of small glands with diameter varying from .5-3 mm. These glands are loosely bound together by a somewhat thickened connective tissue, but in no place does the disease seem to have invaded the capsule.

On the left side of the neck are two masses of glands, an upper bunch situated behind the angle of the jaw and composed of about 20 small and two large glands. The smallest 0.5 mm. in diameter, the largest 6 x 3.5 x 1.5 cm. The lower bunch measuring 10 x 7.5 x 3.5 cm., composed of about 15 large and medium-sized glands, varying in diameter from 2-4 cm. In the lower part of the mass the glands are loosely bound together by a thickened capsule, the upper 3-4 glands cannot be separated.

The anterior mediastinal glands form an almost globular mass with a diameter of 10 cm. This mass is mostly made up of large glands which are rather densely bound together, the disease in places seems to have penetrated the capsule of the glands.

The posterior mediastinal glands are also enlarged but less markedly so. They are discrete and the largest is 3.5 cm. in the longest diameter. The glands on the lesser curvature of the stomach are enlarged and loosely bound together; their average diameter is 2 cm.

The mesenteric glands are but slightly involved, the largest being 1.5 cm. in greatest diameter. The glands at the hilum of the spleen and those in front of and below the pancreas have coalesced into one dense mass. Those at the hilum of the spleen average about 2 cm. in diameter and show many of them a slight greenish-black discoloration, most marked at the periphery.

On section the glands present two distinct appearances—the smaller ones are homogeneous of a whitish-grey color, the larger ones are mottled in appearance, due to irregular areas of a light yellow color. No enlargement of axillary or inguinal glands.

The tonsils are not enlarged.

Pancreas.—Is surrounded by a dense mass of medium-sized glands with average diameter of 1.5 cm. The pancreas itself is apparently normal.

Bacteriological Examination.—Cover slips from the lung showed a few capsulated diplococci.

Cultures from the lung—micrococcus lanceolatus.

Cultures from the glands and viscera, with the exception of left kidney, remained sterile.

Cultures from left kidney contained a colony of streptococcus, and colonies of a fine bacillus, which were not identified.

The tissues were preserved in alcohol and Müller's fluid.

Microscopical Examination.—The lymph glands of the cervical, mediastinal, bronchial, mesenteric and abdominal groups were examined.

The mediastinal glands show a younger and more cellular type of growth than any of the others. The capsule is not especially thickened or infiltrated. The blood-vessels are numerous, full of blood and show no especial structural change. The lymph sinuses are markedly dilated everywhere through the growth. The increase in connective tissue, although not marked in ordinarily prepared specimens, is well shown in sections stained by the Mallory connective-tissue method. Moderately coarse bands of fibrous tissue are then seen dividing up the gland into indefinite lobules; the connective tissue always starts from about the vessels and the lymphatic sinuses, which are here so dilated.

There is but little increase of connective tissue in the more cellular portions of the tumor. The subdivisions of the connective-tissue bands form a fine reticular mesh work, on which lie large epithelioid and uninuclear and multinuclear giant cells. The interstices of the network are filled with numerous giant cells, lymphocytes and blood cells. The giant cells are by far the most numerous element present; their relation is evident to the so-called endothelial cells lying on the reticulum, and which in this case show marked proliferation with the formation of large epithelioid cells with oval vesicular nuclei. The giant cells are found both on the framework and in the interstices, and are abundant in dilated lymph sinuses. They are conspicuously large, often the size of twenty ordinary lymphoid cells. They may appear with connective-tissue processes and with one or many nuclei. The protoplasm is frequently vacuolated. The nuclei of these cells are the most characteristic part of the growth. In form they are large, round or oval; if multiple, often bean shaped. In this specimen they are peculiarly bizarre and irregular. They show evidences of direct division. They contain always one or more large, round, oval or irregularly shaped nucleoli, which have an affinity for acid stains. The chromatin network of the nucleus is usually marked, especially at the periphery. Giant cells with long drawn out and irregularly shaped nuclei are frequently seen in the cell spaces; these suggest the probability of amœboid motion.

The general structure of a lymph gland has been obliterated by the proliferating endothelial cells and by the new growth of fibrous tissue; several remnants of lymph nodes remain. The lymphocytes in such areas are usually of the large variety. The lymphocytes, both of the small and large type, are everywhere abundant, lying in the tissue interstices. Many of the nuclei of the lymphocytes show fragmentation.

A peculiar form of small cell, with a deeply staining protoplasm, is

frequently seen; the nuclei very deeply staining and homogeneous, or consisting of two or three deeply staining particles, apparently fragmenting. It is evident that these cells are degenerating. Very few eosinophilic cells are seen. No plasma cells or "Mastzellen" were observed. One probable "Kugelzelle" seen.

Typical phagocytic endothelial cells are found. Quite a few areas are seen where the cells have undergone a hyaline degeneration, and a few polymorphonuclear leucocytes are invading the necrosed region. There is no evidence of tubercle formation, Langhans' giant cells or caseation. No tubercle bacilli could be found. The degeneration observed here may be due to anæmic necrosis.

The number of lymphocytes with fragmenting nuclei, and cells showing evidence of degeneration, make it evident that the tissue is in the process of fibrosis. The fine cellular elements of the gland are giving place to the proliferation of the fixed connective-tissue cells. A later stage in the pathological process which we find exemplified in the cervical and abdominal glands.

In the cervical glands the connective-tissue bands are coarser, more numerous and break the tissue up into large lobules. The fibrous tissue meshwork is coarser, more abundant and the cellular elements seen in the interstices are fewer in number. We have fewer giant cells and lymphoid cells.

The blood-vessels show considerable endarteritis and periarteritis. The lymph sinuses are still abundant, but also give evidence of the effect of the fibrosis in less dilated spaces. The giant cells are similar but even more bizarre in form and position. Very greatly elongated cells are frequently seen and one typical giant cell was found passing through the wall of a vessel. The lymphocytes are still abundant, but disintegrating nuclei are common.

Mitotic figures are quite frequently seen. No excess of eosinophilic cells appear. A few "Kugelzellen" are seen. Small areas of necrosis appear, as in the mediastinal gland.

Nothing suggesting tuberculosis could be found; no tubercle bacilli were demonstrable.

The mesenteric gland examined seemed normal.

The spleen shows, on examination, macroscopic nodules of similar structure, as the glandular growth, separated by islands of more or less normal splenic tissue. The capsule appears normal; there is no infiltration. The trabeculæ are not especially thickened. Practically no Malpighian bodies are to be seen, although small accumulations of lymphoid cells, partially invaded by new-formed tissue, suggest the remains of such structures. The nodules vary in size from small foci just perceptible with the low power of the microscope to large macroscopic nodules. The structure of the small areas consists of a network of the large epithelioid cells, lying on a reticular foundation, and containing in its interstices lymphoid and giant cells. Very few eosinophiles are to be seen. No plasma cells are found.

The larger areas vary only in being much more fibroid. The connective tissue, as shown in the Mallory stain, predominates, and the free cellular elements are relatively diminished. Most of the nodules show one or more good sized vessels in their interior. The lumen of

these blood-vessels is not occluded but they show periarterial thickening, and are usually the center of the fibroid tissue radiation. The lymph spaces in the tumor mass are dilated. The splenic tissue is compressed about the larger nodules, flattened out tangentially and so forms a partial capsule to the mass. In the more normal portion of the sections the splenic pulp shows very few changes. The sinuses contain many endothelial cells and some of them are phagocytic.

The cellular elements are identical in their morphology to those described in the glandular growth. We also find numerous mitoses, but fewer signs of cellular destruction and nuclear fragmentation. Several "Kugel" were seen free in the tissue spaces and one "Kugelzelle."

The spleen shows considerable golden-brown pigment lying free between the tissue cells.

There are no signs of necrosis, but in several small areas, where the connective tissue predominates, a hyaline degeneration of these cells seems to be taking place.

No evidence of tuberculosis, either in tubercle formation, typical giant cells, caseation or tubercle bacilli, could be found.

There were no lymphomatous changes found in the other organs examined. No tubercle bacilli were demonstrated.

The lung was the seat of extreme bronchopneumonia, which gave no evidence of being tuberculous. The other organs were practically normal.

Case IV.—I. M. White boy, age 17. Admitted March 28th, 1901. Discharged June 15th.

Complaint.—Swelling of neck.

Family History.—No consumption in family. Healthy people.

Personal History.—Only diseases measles, mumps, whooping cough. Denies venereal contagion. Always in good health. Quinsy 7 years ago; dates present illness from that.

Present Illness.—First noticed a small lump, size of hickory nut, which has grown steadily larger. Began 6-7 years ago. Now occupies all right side of neck. Grown faster the last two years. No pain. Since November, 1900, has had night sweats; sometimes every night, and then not for a week. No loss of strength or weight. Appetite good. No cough.

Physical Examination.—Heart and lungs negative. Slightly anæmic. No abdominal distention. Spleen not palpable. Swelling on right side of neck from mastoid process to larynx, 15.5 cm., and 8.5 cm. from maxilla down. Another swelling 4.5 cm. in diameter lies below the larger swelling almost in mid-line. Surface of swelling smooth; no nodules on surface; freely movable. Overlying skin normal. Consistency hard but elastic. No fluctuation; feels solid. No connection with thyroid. String of small glands in front and behind masses described above. No other glandular enlargement.

April 4th.—

Red blood corpuscles	5,000,000
Leucocytes	15,000
Hæmaglobin	60%

CASE I.

CASE V.

CASE IV.

CASE IV.

Count of 550.

Polymorphonuclears	87%
Small mononuclears	2%
Large mononuclears	4%
Eosinophiles	3%
Transitionals	1.6%
Mastzellen	.015%

April 6th. Did not react to tuberculin.

April 22nd. Hæmaglobin 50 per cent.

June 1st. Operation under ether, Dr. Mitchell. Complete excision of glands on right side of neck.

Pathological Description.—Specimen consists of a very large mass of glands, discrete and confluent (see photograph). The largest mass is 12 x 7 x 8 cm. in size. The smallest glands are no larger than a pea. There is considerable variation in the appearence of the cut surface of the glands. The larger glands are greyish and translucent, the smaller ones almost homogeneous and yellowish in color. A few are hæmorrhagic. No foci of necrosis, suppuration or caseation visible. There seems to be less tendency to become confluent than in tuberculosis.

June 15th, discharged. Good result.

Weight, 111½ pounds on admission. On discharge, 120 pounds. Temperature varied from 101 to normal during stay.

Inoculation Experiment.—Two good sized pieces of the cervical gland, of this case, were inoculated subcutaneously into a rabbit on June 1st, 1901. The operation was performed aseptically and the wound healed per primum. The rabbit remained perfectly healthy up to November 11th, 1901, when it was killed.

At the autopsy, there was found at the point of inoculation a mass about 1 x 0.5 cm. in diameter, just beneath the skin and adherent to it. On microscopical examination this mass was found to consist of the degenerated remains of the pieces of lymph glands originally introduced. The disintegrating tissue was encapsulated by connective tissue, and infiltrated and surrounded by numerous leŭcocytes and lymphoid cells. There was no formation suggesting tubercles, no typical tubercular giant cells, and it was impossible to demonstrate tubercle bacilli by the usual staining methods. The adjacent inguinal lymph glands were slightly enlarged.

The axillary, ileocæcal, and retroperitoneal lymph glands were enlarged. Both kidneys and the liver contained numerous abscesses, due to a form of actinomyces, which we do not believe had any relation to the original inoculation. With this exception, the internal organs appeared normal on gross inspection and on microscopical examination.

There was nothing found to indicate a pathogenic action of the material introduced, or that it was of a tuberculous nature.

Readmitted.—November 30th, 1901.

About two months ago patient noticed a small, hard lump about size of pea in right side of neck above the clavicle. This has been growing slowly larger. Is not painful or tender. General health has been excellent since discharge.

Physical Examination.—Well nourished. Mucous membranes of a good color. Examination of thorax and abdomen negative. Spleen is not palpable.

December 5th.—One enlarged gland 7 cm. to right of 7th cervical spine is freely movable under the skin. It measures about 1 cm. in diameter. Entire field of operation shows no recurrence with the exception of the external outer and lower portions, which correspond to supra-clavicular triangle. Here a freely movable, hard, smooth gland can be felt. This gland has grown perceptibly since patient was examined three or four months ago.

Sterno-cleido-mastoid muscle seems practically obliterated on right side, and there seems to be paralysis of trapezius on same side. Spinal accessory nerve must have been cut at former operation.

No enlargement of glands of axilla or other superficial glands.

Examination of urine was negative.

Temperature was practically normal during stay in hospital.

Blood examination, December 4th, 1901, 2 P. M.

Red blood corpuscles	5,250,000
Leucocytes	10,000
Hæmaglobin	84%

Differential count, 500 leucocytes:

Polymorphonuclears	388	77.6%
Small mononuclears	47	9.4%
Large mononuclears	50	10.0%
Transitionals	5	1.0%
Eosinophiles	10	2.0%

Operation, December 7th, 1901, by Dr. Mitchell, under cocaine.

Excision of bunch of small glands from the lower part of the posterior triangle of right side of neck. The glands were superficially situated.

Pathological Description.—Specimen consists of about eight small glands and the surrounding connective tissue. The glands are discrete and freely movable. The largest gland does not measure over 2.5 cm. in diameter, the smallest is only a few mm. in size. The glands are firm but elastic in consistency. On section the cut surface appears greyish, semi-translucent and homogeneous. There are no yellowish areas to be seen, or any suggestion of necrosis. Very little juice can be squeezed from the glands. The capsule does not seem thickened or infiltrated.

Cultures from the glands were sterile.

Inoculation Experiments.—A rabbit and a guinea-pig were inoculated, under aseptic precautions, intraperitoneally, with one-fourth each of the largest gland. A guinea-pig was inoculated subcutaneously with a piece from another gland.

The wounds healed per primum. The animals are still living, one month after inoculation.

The tissues were preserved in alcohol, Zenker's and Flemming's fluids.

Microscopical Examination.—The normal structure of a lymph gland is entirely lost. In the section of a small gland the peripheral portion

seems to have undergone less changes than the central portions; in a few places the remains of the lymph nodes can be made out, lying beneath the capsule. In the older, larger and more involved glands, there is complete uniformity of the tissue structure. In the small glands, there is a great increase near the hilum of vessels, some of these are blood-vessels, but many seem to be dilated lymphatics. Between the vessels are massed lymphocytes and other cellular elements which will be described later. Toward the periphery the vessels become fewer, the stroma finer, the cellular elements more spread out, and cells with large vesicular oval nuclei are more abundant. The appearance of granulation tissue, spoken of by different writers, might be suggested to the casual observer. The increase in connective tissue is more evident in the larger glands, apparently as coarse bands, or irregular masses, and as a fine reticulum, dividing the glandular substance. There is no especial thickening or infiltration of the capsules to be made out.

The large, irregular protoplasmic masses, from which connective-tissue bands are often found radiating, are poor in nuclei, and are found occasionally, including red blood cells and lymphocytes, suggesting in these instances obliterated vessels. In a preparation stained in Ehrlich's triple stain, vessels the center of a connective-tissue foci can easily be made out. The increase of connective tissue, then, seems to start perivascular, and from the changes seen in the small lymph glands would seem to occur first at the hilum, but involves the whole gland by extending gradually peripherally.

The larger vessels show an endarteritis also, and frequently their walls are infiltrated with lymphocytes. With low power, in older glands, dense groups of lymphocytes can be made out, dotted over the section in irregular masses; on closer examination a small vessel is usually seen to be in the center of such a group. These may be the remains of lymph nodes. The finer connective-tissue bands, in turn, break up into a network, whose meshes are filled with lymphocytes and large epithelioid and giant cells. The nuclei of this stroma seem to be of the usual spindle shape found in connective-tissue cells. Disregarding the cells of the stroma and the normal blood elements, in studying this case, we have divided the cells present into the following divisions, under which they will be separately considered:

1. Lymphocytes.
2. Epithelioid cells and large giant multinuclear cells.
3. Eosinophiles.
4. Plasma cells.
5. Giant cells.
6. Kugelzellen, etc.

1. The lymphocytes form the greater part of all the cells present. There is nothing noteworthy in their appearance or arrangement. In this case, few if any remnants of typical lymph nodes could be made out, and in these there was no marked increase in cell division, as figured by Goldmann. Mitotic figures, presumably in endothelial cells, were frequently seen, as would be expected from the marked proliferation of these cells, which is taking place.

2. The next most important and numerous group includes the epithelioid and large multinuclear cells, so conspicuous in the sections. Everywhere among the lymphoid cells filling the tissue interstices we found large cells with large oval vesicular nuclei, having the appearance of connective-tissue cells. These cells in ordinary preparations appear like the proliferating connective-tissue cell of the part and were considered to belong to the reticulum. In the Mallory connective-tissue stain we convinced ourselves that these cells lie on the reticulum, or in the meshwork, we must then suppose them to be proliferations from the endothelial cells normally found there. Such cells are found in great numbers in the dilated lymph sinuses. Transitions between such cells and cells with nuclei almost filling out the whole cell and from these to giant cells, often multinuclear, are clearly made out.

These giant cells vary greatly in size. In shape they may be round or polygonal, according to their position in the tissue. Cells with irregular protoplasmic processes are occasionally seen. The protoplasm is homogeneous, staining deeply in the acid dyes. Fat droplets scattered through the protoplasm and grouped about the nucleus are seen in the Flemming preparations. Vacuolization of the protoplasm is frequently seen in the large cells. The nucleus is always relatively large, filling out at least two-thirds of the cell. There may be as many as six nuclei in a cell; if single it tends to be round or oval. A common form is somewhat bean-shaped, and we often find a cell with two biscuit-shaped nuclei, with the concave sides approximating. The nucleus is vesicular; the chromatin network is well marked; it always contains at least one nucleolus, often a single large nucleolus. In the double stains this always takes a contrasting color to the nucleus, having an affinity for acid dyes.

Frequently bipolar, irregular, barred or chain nucleoli may be seen, probably in cells about to divide. Large cells with partially divided nuclei and irregularly lobed nucleoli were often met with suggesting a direct division. No karyokinetic figures were seen in the large cells, though mitosis in cells corresponding to the large epithelioid cells often occurs. These giant cells were more abundant in the larger and presumably older glands, and lie in the interstices of the stroma. They occur in all parts of the gland, and do not seem to arise especially in any particular locality. They have been seen in blood-vessels.

3. The abundance of eosinophilic cells in these specimens is especially marked. These cells are slightly larger than the ordinary polymorphonuclear leucocyte. Their protoplasm is closely packed with large refractive granules, staining deeply in acid stains. The nucleus is relatively small, usually single, round or two-lobed. Frequently cells with two or three round nuclei are found. The nuclear structure is almost homogeneous, showing no chromatin network or nucleoli, and staining deeply in the basic stains. No karyokinetic figures were seen in such cells, or any suggestion of division.

The eosinophiles seem to be more numerous around vessels, and in the connective-tissue stroma about obliterated vessels. The area containing the greatest number of eosinophiles in these sections was singularly free from giant cells. The eosinophiles were found in the reticular spaces or in the connective-tissue stroma. As many as thirty-

five were seen in one oil-immersion field. There were no blood-vessels in this area.

Occasionally eosinophiles were found in a blood-vessel, but not in abnormal numbers. The foci of lmphocytes grouped about small blood-vessels, and the remains of what was thought to have been a germinal centre were free from eosinophiles. The eosinophiles are not numerous in the capsular tissue, but are frequently found aggregated beneath it, in as large or in larger numbers than elsewhere.

4. *Plasma cells* are frequently found lying between the lymphocytes. They are not nearly as abundant as in some other cases. Groups of plasma cells are found occasionally in the capsular tissue and in the connective tissue at the hilum. No "Mastzellen" cells were seen.

5. *Multinuclear* giant cells, entirely different from the giant epithelioid cells, were occasionally seen in these glands. They suggested the typical Langhans' cell; homogeneous protoplasm, and numerous small, oval vesicular nuclei, usually arranged peripherally. The formation of such cells by fusion was not determined, as in Case V, but is probable.

6. The cells mentioned by Goldmann as frequently found in this disease, called "Kugelzellen," were fairly abundant through these sections. In Ehrlich's tri-acid stain, large cells having a golden-red protoplasm made up of large irregular droplets with a small indefinite nucleus and cells containing large golden-red masses, but having no visible nucleus, were frequently found lying between the connective-tissue cells, usually in vacuoles. No relation between these cells and the blood-vessels, or the other cellular elements could be made out. These "Kugelzellen" are well demonstrated by the Weigert fibrin, Biondi-Heidenhain, Van Gieson, and Borrel methods of staining, but in ordinary hæmatoxylin and eosin specimens stain too densely to be distinguished.

No micro-organisms could be found in the specimens. There were no areas of necrosis, or any formation suggestive of tuberculosis. Several specimens were stained for tubercle bacilli, but none were found.

Microscopical Examination (2d operation).—A section of the largest gland removed at this operation gave a wonderful picture of the early stages of the pathological process. Fortunately, in the capsule of this gland, which itself was not over 1.5 cm. in diameter, was found a small gland not over two millimeters in length.

This furnished the smallest specimen of gland yet examined, and as we believe, the very beginning of the histological changes. The outline of the lymph nodes and the medullary cords are still almost normal. The lymph sinuses are not especially dilated, but are partially filled with cells. These cells, which are the most noticeable change from the normal, consist of large epithelioid cells, evidently proliferation from the endothelial cells covering the reticulum of the sinuses. A few of these cells are phagocytic and contain leucocytes in their protoplasm. In structure they are quite uniform, three or four times the size of a small lymphocyte; the protoplasm is almost homogeneous and stains well in the acid dyes. The nucleus is oval or bean-shaped, relatively large for the size of the cell, vesicular in appearance, having a well-marked chromatin framework and one or more small nucleoli. These

cells are found still attached to the walls of the sinuses, or free in the lumen or intracellular spaces. The lymph nodes show in their germinal centres similar large cells, and mitotic figures in these areas are common. We do not find as yet any giant cell formation from these proliferating endothelial cells. The lymph sinuses also are crowded with lymphoid cells, mainly of a small uniform type. There is evidently an increase in the number of these cells, and we also find numerous plasma cells among the lymphoid cells of the nodes and the cords of the gland.

Quite numerous eosinophilic cells appear among the lymphoid cells of the cellular portions; these are not usually seen in the sinuses and none are found in the germinal centres.

The blood-vessels are not especially increased. There is no perceptible change in the capsule, or in the fibrous framework of the gland.

There are no signs of acute inflammation in the tissue; very few polymorphonuclear leucocytes were seen. In the center of a swollen germinal centre one large cell full of irregular, small kugeln was observed.

The large gland, itself only about 1.5 cm. in diameter, shows similar but more advanced changes. The ordinary gland structure is lost, due mainly to obliteration of the distinction between the lymph sinuses and the nodes and medullary cords, by the filling up of all the free spaces of the gland with the proliferating cells. These cells consist mainly of lymphoid cells and giant cells, as described in the small gland, but the pathogenic action has been of a more extensive nature. We find here numerous large giant cells, obvious derivations from the proliferating endothelial cells. They are very numerous, lie mostly in the free cellular spaces, and are found in the swollen germinal centres of the remaining nodes. They are mainly uninuclear, the nucleus is very large, filling out the cell, the chromatin network heavy, and the nucleoli characteristically conspicuous.

In this specimen, mitotic figures were frequently seen in large cells still adherent to the walls of the lymph sinuses, and also in large cells in the tissue spaces. A few multinuclear giant cells were seen. Numerous lymph nodes were still visible, the germinal centre full of large swollen epithelial cells with frequent mitotic figures. The increase in lymphoid cells was marked, relatively they were in much greater number than in the larger glands of other cases, and of a uniform small type.

Plasma cells were frequently seen, especially just beneath the capsule of the gland, and quite numerous "Mastzellen" lying among the other free cells were demonstrated in the polychrome methylene blue preparations.

Large cells full of bodies resembling the "tingible Körpern" of Flemming were occasionally seen. No definite nucleus could be made out in such cells.

In gentian violet preparations large cells with the protoplasm full of deeply staining granules were occasionally met with.

The lymph sinuses beneath the capsule were large and dilated and full of lymphoid and epithelioid cells. Very few phagocytic endothelial cells were observed. The lymphatic channels were numerous and

dilated throughout the bulk of the gland. The blood-vessels were numerous, although small, and were full of blood.

In the Mallory connective-tissue stain, the beginning increase in the connective tissue was obvious. Starting from about the vessels and sinuses, where quite coarse bands are formed, it radiates in a fine network throughout all the gland, the lymph nodes showing the least increase in the fibrous framework. This specimen showed plainly that the epithelioid cells only lie on the reticulum and are not the cell bodies furnishing their fibres. Definite connective-tissue nuclei were frequently found in the stroma. It is interesting to note how early this fibrosis begins, for this gland is undoubtedly of the cellular or soft type, and one would not believe in ordinarily stained specimens how great was the increase in the connective tissue.

The number of eosinophiles present was surprising. In some fields they equal or exceed in number all the rest of the cells present. They showed invariably a rather homogeneous nucleus, consisting of two or three balls or lobes, and the usually heavy granulation of the protoplasm. No suggestion of division of the nuclei or cells showing beginning granulation was ever observed. The germinal centres of the nodes were remarkable for being practically the only portion of the glands not invaded by these cells. They were practically never found in the center of the lymph nodes, although very abundant in the periphery.

No especial relation of the eosinophiles to vessels could be made out. They were not found in the capsule, which was in fact apparently normal. In the area in which there is greatest cell proliferation, represented probably by the original lymph sinuses, the eosinophiles seem to be the most abundant.

In one section several large giant cells, the size of a half dozen of the usual epithelioid giant cells, were observed. These cells showed homogeneous, very deeply staining protoplasm and numerous small oval peripherally arranged nuclei. They suggest the pictures given by Ribbert of giant cells formed by coalescence of the reticular cells.

No tubercle bacilli were demonstrated, no tubercle formation or areas of necrosis were observed.

No micro-organisms of any description were found.

Case V.—J. B. White boy, aged 11 years, admitted to the Surgical service, The Johns Hopkins Hospital, January 19th, 1899.

Complaint.—Swelling on right side of neck.

Family History.—Father died of consumption; mother has a bad cough. History negative.

Past History.—Scarlet fever two years previous. An attack of "heart disease" with swelling of the feet one year after, during which time he was in bed a month. Has always been a mouth breather. Has never been sick in bed but once.

Present History.—A swelling appeared on right side of neck about three years ago. Does not remember the original size but thinks it has doubled in size in the last year. Causes him no inconvenience, no pain and is not tender on palpation. Has no cough or expectoration. Appetite is poor.

Physical Examination.—Rather undersized boy. Weight 61 pounds.

Chest poorly developed; costal angle less than 90°; expansion slight but equal. Lungs negative on auscultation and percussion.

Heart.—No increase in area of cardiac dulness. Soft systolic murmurs heard at apex and over body of heart. Second pulmonic sound accentuated. Pulse slightly irregular.

Spleen.—Not palpable. Abdomen soft, everywhere tympanitic.

Glands.—On right side of neck the glands are enlarged and soft, varying in size from small hen's egg to a pea. Glands are discrete and closely adherent to the underlying tissues but are not bound to the skin. Swelling extends from within 1 cm. of mid-line in front to 3 cm. from mid-line in back, and from the level of the lower part of the ear and angle of jaw almost to the clavicle. The largest gland is just below and posterior to ear.

On the left side of the neck, in the submaxillary triangle, just below the angle of the jaw, there are several glands, the largest of which is 1-1.5 cm. in diameter. Posterior cervical glands are slightly enlarged.

Axillary and inguinal glands are palpable on both sides.

Right epitrochlear can be felt.

Tuberculin .002 grms. given January 20th without reaction.

January 21st. Blood examination:

Red blood corpuscles	4,896,000
Leucocytes	12,000
Hæmaglobin	70%

Differential count, 250 leucocytes:

Polymorphonuclears	80.8%
Small mononuclears	13.6%
Large mononuclears	1.6%
Transitionals	2.4%
Eosinophiles	1.6%

January 28th, 1899. Operation by Dr. Cushing under ether anesthesia: glands excised in one complete mass.

Pathological Description.—Dr. Elting. Specimen consists of a mass of glands removed from the right side of the neck. The glands vary in diameter from 0.5 to 4 cm. Nowhere do the glands seem to be adherent to each other, easy separation of the glands from each other is possible. On section the cut surface presents a greyish, translucent, fairly homogeneous appearance. Any differentiation of cortex and medulla is impossible. In the substance of some of the glands there are small hæmorrhages, due to transudation at operation.

Wound healed per primam. Patient's condition improved while in hospital.

February 9th, hæmaglobin 80 per cent, red blood corpuscles 4,620,000.

Examination of urine negative. Temperature varied from 97.5°-100.2° without regularity in the exacerbation.

Readmitted January 8th, 1901.

Present Illness.—2-3 months after operation the glands on right side began to enlarge again and have steadily increased in size. No difficulty in swallowing or breath. No pain. Has a slight cough; no expectoration.

General Physical Examination.—As on first admission.

Glands.—A mass of enlarged glands extend from the lower attachment of the ear along the lower jaw. Glands are freely movable, not matted together, not painful or tender. The largest is 2 cm. in diameter. Consistency firm, not very hard. A chain of smaller nodules runs down toward the shoulder.

On the left side of the neck 2-3 small glands are palpable in the submaxillary triangle.

Axillary glands are not enlarged but are palpable. Inguinal glands are normal.

February 2nd, 1901.—Operation by Dr. Mitchell under ether anesthesia. Complete excision of the glands on the right side of neck. The enlarged glands extended up under jaw, along the internal jugular vein, in the posterior triangle and behind the clavicle. The glands were located in the site of the old operation and beyond its limits.

Wound healed perfectly.

Pathological Report.—Dr. Yates. Specimen consists of a mass of glands removed from neck and submental region. There are a dozen or more glands varying in size from a hen's egg to that of a lima bean. These glands are discrete and not matted together, being fairly movable in the surrounding connective tissue. There is some hæmorrhage in the glands, but more or less punctate. The larger glands on section show a uniform greyish semi-translucent surface, through which are scattered firm yellowish areas. These points suggest caseation, but they are firm and hard on further examination. Almost no lymph can be squeezed from the tissue. The smaller glands present a more homogeneous greyish opaque surface. Nothing suggesting necrosis was observed.

January 9th. Blood count:

Red blood corpuscles	4,208,000
Leucocytes	6,100
Hæmaglobin	90%

Differential count, 502 leucocytes.

Polymorphonuclears	71.8%
Small mononuclears	5.6%
Large mononuclears	17.4%
Transitionals	.6%
Eosinophiles	1.2%
Mast zellen	.8%

Temperature varied irregularly from 96°-101°; pulse from 60-110.

January 24th. .002 grms. tuberculin given without perceptible reaction.

February 12th. Discharged.

December 6th, 1901. Boy returned for examination.

General condition fair. Appears undersized for his age, but claims to feel perfectly well. Is earning his living in a box factory.

In the area of the extirpation, on the right side of the neck, there is no recurrence of the glandular enlargement. Just above the middle of the right clavicle a bunch of small glands can be made out, the largest several cm. in diameter.

On the left side of the neck below the ramus of the lower jaw is a globular swelling the size of a small pear. On palpation the mass is found to be made up of numerous small, discrete glands, which are freely movable under the skin and over the underlying tissue. The swelling is painless and does not increase in size.

There is no apparent enlargement of the other superficial glands of the body.

Blood examination, December 7th, 11 A. M.

Red blood corpuscles	4,984,000
Leucocytes	8,200
Hæmaglobin	80%

Differential count, 500 leucocytes:

Polymorphonuclears	407	81.4%
Small mononuclears	40	8.0%
Large mononuclears	32	6.4%
Transitionals	6	1.2%
Eosinophiles	15	3.0%

Microscopical Examination. Different pieces of the glands removed at the first and second operations, in January, 1899, and January, 1901, were examined. The tissues were preserved in alcohol. As the histological findings were practically the same only one description will be given.

The normal lymph gland structure has disappeared; in a few places lymph nodes can still be discovered. The capsule is not thickened or infiltrated. No eosinophilic cells are found in the capsular tissue but they are noticeably abundant just beneath it. In the smaller glands distended lymph sinuses are numerous. These sinuses are filled with lymphocytes, polymorphonuclear leucocytes, red blood cells and many phagocytic endothelial cells. These endothelial cells have an oval densely staining nucleus relatively small for the size of the cell. Large giant cells are also found in these sinuses. The vesicular nucleus or nuclei of these cells is relatively very large, their protoplasm is occasionally vacuolated but they are never phagocytic. The blood-vessels in the small glands are numerous, large and full of blood. The small vessels frequently show an endarteritis, which may cause complete obliteration of the lumen. The increase in connective tissue throughout the glands is very marked. There is not the coarse radiation from about the periarterial tissue, noticeable in other cases; here the increase, though excessive in the large glands, is uniformly diffuse throughout the tissue. We do not find the islands of cellular tissue cut off by coarse connective-tissue bands as in other specimens.

In the large glands the connective tissue shows in places hyaline transformation. The cellular tissue, exclusive of this fibrous increase, consists of large epithelioid cells with large vesicular swollen nuclei. Occasionally such a cell is found with a nucleus, showing a marked constriction suggesting direct division. Lymphoid cells in great numbers fill the interstices between the epithelioid cells. The small lymphocytes predominate, and there is great uniformity in their size. Large lymphocytes do occur, but no plasma cells were seen. Mitoses in cells about the size of the large lymphocytes are frequently observed. Nuclear fragmentation is also met with.

Two varieties of giant cells are found in these glands.

One which we are in the habit of calling the giant lymphoma cell occurs in great numbers singly and in groups in the interstices between the cells forming the stroma of the gland. They are also met with on the stroma, showing by their branching, protoplasmic processes, their relation to the epithelioid cells previously described. The protoplasm of these cells is often granular, occasionally vacuolated. The nucleus is relatively very large, it may be single, is more often double, but three or four or more nuclei are occasionally met with. The nuclei are usually round or oval, bizarre forms are probably often due to the hardening fluid. The chromatin network is marked, and large round or oval nucleoli, either single or multiple, are always to be seen. Nuclei showing distinct division are frequently met with. The staining properties of the cell are noticeable, the nucleoli taking a red stain in ordinary hæmatoxylin and eosin preparations.

The second form of giant cells at first glance seem to be of the Langhans' type. They are very large; in the ordinary stain show an irregular cell outline and numerous, rather small, epithelioid nuclei. They frequently contain vacuoles. In the triple stain it is clearly shown that these cells arise from the coalescence of the large cells of the stroma, the protoplasm showing a hyaline change. In some instances the different cell outlines can be clearly distinguished. Diligent search was made for tubercle bacilli, but none could be found. Eosinophilic cells, showing single or double lobed nuclei, are, as before said, numerous. No relation to the vessels was made out. One eosinophilic cell was found passing through the endothelial lining of a blood-vessel. No mitoses were ever observed in these cells. No "kugeln zellen" were seen.

Large cells, the protoplasm taking a deep acid stain, with a single dense nucleus, were occasionally met with. We did not observe any areas of necrosis or of cellular degeneration except the slight hyaline changes already mentioned.

A rabbit was inoculated subcutaneously with a piece of the cervical glands extirpated January 2nd, 1901. It died February 15th.

At the autopsy the rabbit appeared well nourished. The incision at the seat of inoculation had healed perfectly. Just under the scar were several masses which proved to be the degenerated remains of the piece of gland originally introduced.

The tissue in the neighborhood showed no signs of inflammation. The neighboring lymphatic glands were slightly enlarged, but on section showed nothing abnormal. No tubercle bacilli were found.

The organs were apparently normal. Smears and microscopic sections failed to reveal any tubercle bacilli or signs of tuberculosis. The cause of death was not ascertained.

Case VI.—W. Q. White, age 7 years. Admitted to The Johns Hopkins Hospital, service of Dr. Halsted, August 17th, 1897.

No history was obtained as the parents did not visit the child.

Physical Examination.—Well nourished, well built child; appears anæmic. Is able to play with other children, is not especially weak.

Lungs.—Negative on examination.

Heart.—Blowing systolic murmur quite localized at apex, although audible at pulmonic region and in the axilla. No cardiac enlargement.

Liver.—Dullness begins at lower border of fifth rib and extends to three cm. below costal margin. Edge is palpable but no nodules are felt (see photo).

Spleen.—Dullness is increased, edge is easily felt and is hard.

Glands.—All the glands of the right side of the neck are enlarged. Posterior cervical chain are the largest, varying in size from 1-3 cm. in length. Supraclavicular and submental glands, with these posterior cervical glands, form a prominent nodular mass. This mass seems freely movable on the underlying tissues, is painless to the touch, and is firm but elastic in consistency. In the right axilla two large glands can be felt. Glands in the left axilla just palpable. Glands of groin not enlarged.

Blood examination:

Hæmaglobin	60%
Leucocytes	11,000
Red blood cells	3,300,000

Differential count by Dr. McCrae, reported normal.

Examination of urine normal.

Temperature on admission 100.4°, varied from this to subnormal during stay in hospital. Pulse varied from 90-135 a minute. Tuberculin administered without reaction. Fowler's solution given after operation.

Operation.—August 24th, by Dr. Cushing, under ether anæsthesia. Complete excision of the glands of right side of neck. Patient stood operation well. Wound healed per primum.

Examination of Specimen.—Entire mass comprises about twenty discrete glands, very firm, encapsulated and non-adherent to surrounding structures. The largest gland measures 4.5 x 3 x 2 cm., the smallest 0.5 cm. in diameter. The capsules are tensely stretched, the glandular substance bulging on section of the capsule and yet on attempting to strip off the capsule it is found to be adherent. On section the glands are homogeneous tawny colored, semi-translucent, without apparent division into cortex or medulla. As a rule, no follicles could be made out. All of the glands show a division by irregularly anastomosing lines of more translucent tissue which is depressed between the bulging, greyish, more opaque portion making up the bulk of the gland. Immediately beneath the capsule of one of the large glands the tissue is soft and partly diffluent.

No signs of inflammation, no areas of caseation nor of hæmorrhagic injection.

September 4th. Discharged.

Child reported some time after this; swelling had then returned under angle of jaw. Since then he has not been at the hospital and it has been impossible to find him.

Microscopical Examination.—The tissue was very old and poorly preserved in alcohol, making the histological examination unsatisfactory.

The gland structure is completely lost. No lymph nodes are visible. The capsule is only slightly thickened and not infiltrated. There is

CASE VI.

CASE VII.

CASE VII.

considerable uniform increase of the connective tissue but in a rather delicate stroma. There are some heavy bands of fibrous tissue, causing a coarse lobulation of the gland. The vessels are abundant and the connective-tissue increase radiates from the perivascular tissue. The blood-vessels are small, and show periarterial thickening, except in the capsule, where the vessels are large and numerous. The lymphatic channels are not especially dilated.

The stroma is full of large epithelioid cells and lymphocytes which are the predominating elements. The lymphoid cells are of a uniform small size. No plasma cells were seen.

Eosinophilic cells were found in great numbers, apparently uniformly distributed, but with slight tendency to congregate about the blood-vessels. No eosinophiles were observed in the capsule, nor were they especially numerous just beneath it. They corresponded exactly to the eosinophilic cells previously observed in similar tissues. In some preparations their nucleus, which usually consists of one or more homogeneous spherules, could be seen to contain a definite nucleolus. Large giant cells, containing one or more large nuclei, were numerous, and showed definite relationship to the proliferating epithelioid cells previously described. The large prominent nucleoli, and the marked chromatin network of the nucleus form a characteristic picture.

A few very large cells, taking a deep acid stain and containing numerous small oval nuclei, were seen. They evidently bore no relation to the large multinuclear giant cells.

There were no areas of necrosis, nor signs of degeneration or tuberculosis. No tubercle bacilli or other micro-organisms could be found.

Case VII.—W. D. M. White boy, age 5 years. Admitted to The Johns Hopkins Hospital, service of Dr. Halsted, June 9th, 1899.

Complaint.—Lump in right side of neck.

Family History.—Negative. No history of tuberculosis or malignant neoplasm.

Past History.—Measles and chicken-pox. No other diseases. Always been healthy and well.

Present Illness.—Nineteen months before admission father noticed a lump, the size of a small nut, back of the right mastoid process. The lump at first grew slowly, but for the last four months has increased in size rapidly. The child has complained of slight pain in the tumor twice. Growth is not especially sensitive to pressure; has never been red or inflamed. Father thinks the growth varies in size.

Condition on Admission.—Fairly well developed, well nourished boy. Mucous membranes rather pale. There is a tumor mass occupying the entire right side of neck, from the mid-line in front to the vertebral spines behind. Tumor measures 21 x 11 cm. The circumference of neck is 37 cm. Skin over mass shows no redness or sign of inflammation, but in many places shows distended veins. The tumor is irregular in outline, seems to be made up of glands fused together, though some, especially along the clavicle and at the angle of the jaw, have remained discrete. The prominent portion, from the mastoid process to the clavicle, is more regular in outline, and gives distinctly the sense of fluctuation. No pain or tenderness can be elicited on palpation. Skin

is nowhere adherent to the mass. The glands on the other side of the neck are not especially enlarged. Glands in axilla and groin palpable.

Thorax well formed; costal angle good. Lungs practically negative on auscultation and percussion. Heart apparently normal. Abdomen, negative. Neither liver nor spleen apparently enlarged. Patellar reflexes increased.

Blood count:

Red blood corpuscles	3,232,000
Leucocytes	14,000
Hæmaglobin	55%

June 16th, differential count:

Polymorphonuclears	46.4%
Small mononuclears	38.6%
Large mononuclears	2.0%
Transitionals	7.8%
Eosinophiles	2.0%
Corpuscles about size of a transitional with deep staining homogeneous protoplasm	2.0%

Urinary examination negative.

June 24th, operation by Dr. Cushing, under ether anæsthesia.

Excision of large mass of discrete glands. All but one gland removed in one piece. A small gland near submaxillary gland was overlooked until the last and was broken during removal. The glands were discrete, encapsulated and not adherent. Cut surface was succulent, not homogeneous. Trabeculæ of œdematous fibrous tissue pass through the glands, and yellowish-white pale areas are irregularly distributed through the gland. No sign of caseation. The glands descended into the mediastinum. Wound healed perfectly.

July 5th, leucocytes 14,000, hæmaglobin 38 per cent. Spleen palpable

Temperature was irregular, 101° on admission; was slightly above normal until after operation, when it rose to 101.8°, on the 6th day, and remained constantly from 100°-103.5° for several days, then gradually sank, reaching normal on discharge. Pulse constantly over 100.

Discharged July 8th, 1901, condition improved.

Boy died seven weeks after discharge, with the symptoms of dropsy.

Pathological Report.—June 24th, 1899, Dr. Sands. The specimen consists of a number of glands, removed with the intervening connective tissue in one piece from the right side of the neck. There are about 55 separate glands, arranged so as to suggest a bunch of grapes. They range in size from those as small as a pea to the largest one which measures 4.5 x 7 cm. All are bound rather firmly together by connective tissue, which contains a small amount of fat and is apparently normal. The glands are firm in consistency with no evidence of breaking down.

For the most part, each gland can be readily shelled out of the connective-tissue surroundings, but in a few instances two or three have grown together, and no line of demarcation can be seen between the individual glands.

The cut surfaces of the glands present slightly different aspects. The largest gland shows on section a distinctly alveolar structure. The

tissue is yellowish in color, firm and somewhat resilient on palpation. A pale thin fluid can be scraped off on the knife blade. A distinct, closely adherent capsule existed in all cases. Running in from the outer margin are several pale translucent lines which divide the surface into four or more lobules, from these again run firm bands which give the surface the fine alveolar appearance. No granular material can be expressed from these alveoli. One medium-sized gland shows much the same structure as that above described, but it is deeply injected, so that the surface has a dull greyish-red appearance. The alveoli contain the same yellowish firm material. The inter-alveolar spaces are hæmorrhagic. Occasionally fatty areas are seen. A sero-sanguinous fluid exudes on pressure.

The smaller glands, measuring 1.5 x 2.5 cm., correspond closely to the large glands, but are more likely to contain hæmorrhagic areas and small yellowish streaks of fat. The tissue is firm, yellowish or reddish in color and alveolar in appearance. Capsules are always present, but not readily separated. Some of the smaller glands are much softer than the others. The alveolar arrangement is not so evident and a greyish granular material can be scraped off from the cut surface.

Patient died July 18th, at his home. The glands on both sides of the neck had begun to enlarge.

Microscopical Examination.—The sections of this case show small lobes of lymphoma tissue separated by broad fibrous bands, including considerable fat. These bands are poor in cells, very few nuclei are visible.

From this encapsulating connective tissue coarse bands pass into the glandular substance and divide it into several smaller masses. A firm but abundant connective-tissue network radiates out from these bands and pass in all directions through the tissue. Very few blood-vessels are seen, and the lymphatic channels are not numerous or dilated. There is no invasion of the capsule by lymphoid cells.

The tissue has lost all resemblance to a lymph gland. No follicles can be made out. Lymphoid cells, plasma cells, epithelioid cells, and giant cells fill the interstices of the connective-tissue framework.

The lymphoid cells are of the usual small type. The plasma cells which are abundant show frequently peculiarities in the form of the nucleus. Nuclei staining in heavy clumps, and then clumps without preservation of the nuclear form, are seen in these cells.

Such fragmentation is frequently observed in cells included in the coarse fibrous bands. This is evidently the beginning of cellular degeneration.

Epithelioid cells, with oval vesicular nuclei, and large giant cells, with one or more large nuclei, are present in great numbers. The heavy chromatin structure of the nucleus, and the prominent nucleoli in these cells, are characteristic. The relation of these cells is not clearly made out in this specimen, as they are poorly preserved. They are often seen to have protoplasmic processes like connective-tissue cells. Eosinophilic cells occur in portions of the gland, sometimes equalling a third of the cells present. They are totally absent in other portions. No especial arrangement about blood-vessels could be seen, but they did occur in greatest number near the periphery of the gland. In polychrome methylene blue specimens, their nuclei, which consist

usually of one or more spherules, take a pale greenish tint, the other nuclei being a definite deep blue.

One cell full of irregular, deeply staining granules was observed in a methylene blue preparation. No "Kugelzellen" were seen.

No areas of degeneration, or anything suggesting tuberculosis, was observed. No tubercle bacilli could be found.

Case VIII.—T. S. White boy, age ten years. Admitted to The Johns Hopkins Hospital, service of Dr. Halsted, March 23rd, 1898.

Complaint.—Enlarged glands of neck.

Family History.—Negative. No history of tuberculosis or cancer.

Past History.—Has had measles, whooping cough and a fever, probably typhoid; otherwise no illness.

Present Illness.—First noticed small pea-sized, hard, movable nodule, just under skin behind the right angle of the jaw, about two and a half years ago. In 3-4 weeks several nodules lower down on same side of neck. Six months ago he first noticed nodule on left side of neck, which comes and goes. These glands grew slowly, and about eight months before admission they were removed by family physician. Since this operation the glands have again increased until they are about the same size as on removal. Glands in left axilla were noticed about one month ago. General health good.

Condition on Admission.—Fairly well developed, well nourished boy. Mucous membranes of good color. Head is pushed slightly to left by a mass of enlarged glands, extending from the mastoid process of the clavicle and from the sterno-cleido-mastoid to the trapezius muscle on the right side. The glands are discrete and freely movable. Seem to be divided into two bunches by a central constriction. The lower group is the larger and extends over the clavicle. Scar of old incision at lower part. The glands are hard and so freely movable that they feel like a bag of marbles.

A few pea-size discrete glands are found in the left post cervical triangle. Glands of groins and axilla enlarged to size of pea.

Spleen and liver not palpable.

Heart apparently normal.

Examination of lungs negative.

Leucocytes 8000.

Differential count 300 leucocytes.

Polymorphonuclears	74%
Small mononuclears	11%
Large mononuclears	10%
Eosinophiles	5%

Examination of urine negative.

April 1st. Operation by Dr. Finney, under ether anesthesia.

Entire mass of glands excised. Measured 16 x 8 cm. With the exception of two or three glands, they were removed in one piece. The glands vary in size from a few mm. in length to several cm. in diameter. The glands are all discrete, firm, elastic, not very hard and vary in consistency. In one place there is a mass of scar tissue 2-3 cm. in diameter, which seems to be infiltrated with lymphoid tissue.

On section, some of the glands show a mottling of translucent and opaque areas, others are of a uniform semi-translucent appearance

with a slight suggestion of a fine granulation. Some are slightly hæmorrhagic. The large glands are more opaque and seem, on section, slightly lobulated. No signs of caseation or necrosis.

Wound healed perfectly. A gland was discovered near the upper part of the incision which had not been removed.

Temperature varied from 100.2° to normal, during entire sickness, but was not regular at all. Pulse from 60-100.

Tuberculin .002 grms given without reaction.

April 12th, discharged.

Microscopical Examination.—Sections of this specimen were not very satisfactory, owing to the age of this tissue and the hardening fluid used (alcohol).

The capsule was much thickened, and in places enclosed areas of lymphoid tissue. The gland was broken up in coarse divisions by bands of fibrous tissue, which had undergone a hyaline transformation. The general connective-tissue framework was uniformly thickened, but without the formation of such coarse strands as in other cases.

The blood-vessels were numerous, many however were obliterated. There was a general periarteritis. At the periphery of the gland, the lymph spaces were large and full of endothelial cells and lymphocytes. A few large multinuclear cells were seen in these vessels.

Several lymph nodes were preserved; these showed the usual proliferation of epithelioid cells. Otherwise the gland had lost its characteristic appearance, and consisted of a coarse connective-tissue framework, in which lay numerous lymphocytes and epithelioid cells. The morphology of the epithelioid cells was not as clear in this specimen as in some others. Large cells, with characteristically large prominent nuclei and nucleoli were found in great number between the other cells. No Langhans' giant cells were seen. Polymorphonuclear eosinophiles appeared in moderate number. No plasma cells were observed. Mitotic figures in large cells were often seen. In one section a large area of necrosis consisting of degenerated cells and fragmented nuclei was found. The vessels in the neighborhood were full of polymorphonuclear leucocytes, and there was considerable infiltration of these cells. This degenerated focus was filled with Russell's fuchsin bodies of varying size. A few indefinite coccoid forms were shown by Gram-Weigert stain.

No tubercle bacilli could be demonstrated.

Since finishing this study, a very interesting case has come under our observation.

The patient was a white boy, eight years old, who was admitted to the surgical wards of the Johns Hopkins Hospital in October, 1901. He complained of swelling of the left side of neck. His family and personal history were negative.

He first noticed the swelling in his neck in February, 1901, when it was as large as the end of his thumb. By July it had increased to the size of a goose egg. The growth was painless, freely movable, and showed no evidence of inflammation. His family physician in July removed the tumor mass. The wound never healed and there has been an open sore in the line of the incision ever since.

The examination of the patient showed an irregular nodular mass

lying over the sterno-cleido-mastoid, but apparently not connected with the deeper structures. The skin surface over this growth was ulcerated. A few enlarged glands were found surrounding the growth and in the left axilla. The glands on the right side of the neck were slightly enlarged. The physical condition of the patient was otherwise excellent.

His temperature was not elevated above 100°. Tuberculin was administered twice, but without reaction. The growth was thought to be sarcoma.

November 13th, Dr. Mitchell removed as much of the growth as was possible. It had extended into the brachial plexus and could not all be taken away. The incision healed slowly but completely.

The microscopical examination, made by Dr. Winne, showed a great mass of inflammatory tissue, at the base of which, and lying near the muscle, was an area of a quite different nature. The tissue here consisted of lymphoid cells, polymorphonuclear leucocytes, swollen epithelioid cells, and numerous large giant cells. The eosinophiles were in very great number in this portion of the tumor, but nowhere else in the section. The giant cells were of the characteristic type described in the previous eight cases. This island of tissue was macroscopically easily distinguished from the rest of the growth. There was no doubt that this was the specific lesion of Hodgkin's disease. The nature of the original growth was thus established. The enlarged glands in the neighborhood showed only the simple changes of chronic inflammation.

As far as we know, this is the first case in which the diagnosis of Hodgkin's disease has been established by the histological examination.

We have also had the opportunity of making this diagnosis in the case of two other hospital patients, by the microscopic examination of single glands extirpated for this purpose. The clinical features of these cases bear out the diagnosis.

DESCRIPTION OF PLATES.

Fig. 1. Greenough-Zeiss. Section of liver from Case I, showing single and conglomerate lymphomatous masses of various size. The compression of the intervening liver tissue, by the expansion of the growth, is evident. The large blood-vessel seen in the lower portion of the drawing, is invaded by the growth, which projects into the lumen and partially fills it.

Figs. 2 and 3. Oc. 3, obj. 6, Leitz. Represents the characteristic histology of Hodgkin's disease. Swollen "endothelial" cells are seen lying on the fibrils of the reticulum. In the interstices of the stroma are found lymphocytes, eosinophiles and large epithelioid giant cells.

Fig. 4. Oc. 3, $\frac{1}{12}$ oil immersion, Leitz. The so-called endothelial cells with their branching protoplasmic processes in different stages of proliferation. Transition from uninuclear giant cells, originating from such endothelial cells, to large multinuclear giant cells are represented, showing the peculiar vesicular nuclei, prominent nucleoli, and protoplasmic processes.

Fig. 5. Oc. 3, $\frac{1}{12}$ oil immersion, Leitz. Lymphatic vessel in the lymphomatous tissue, through the wall of which a characteristic giant cell is passing by its own amœboid motion.

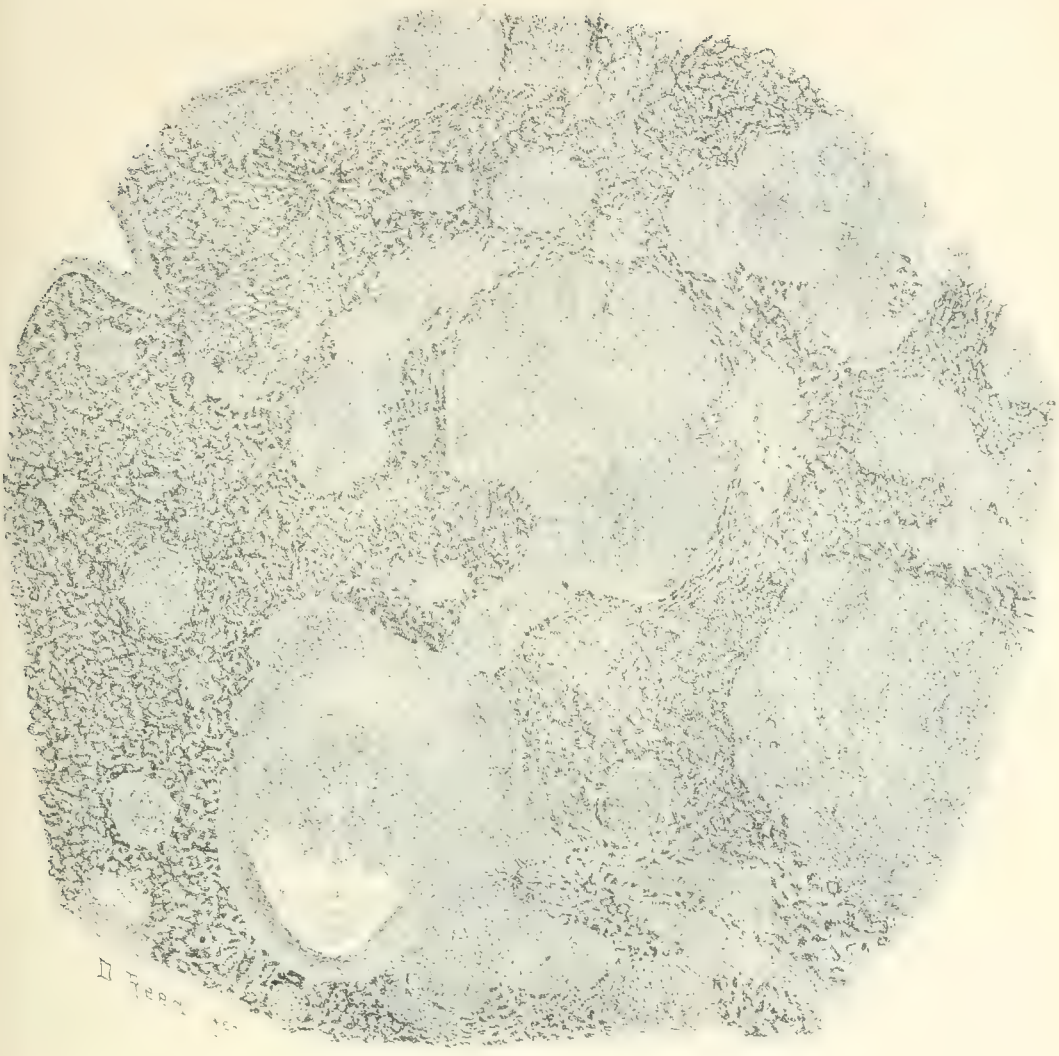

FIG. 1.

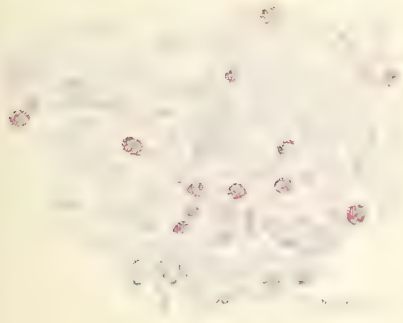

FIG. 2.

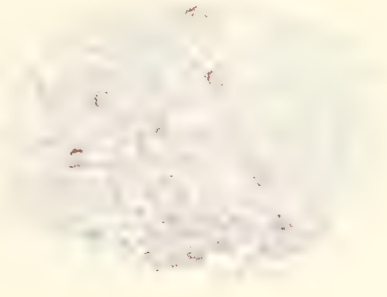

FIG. 3.

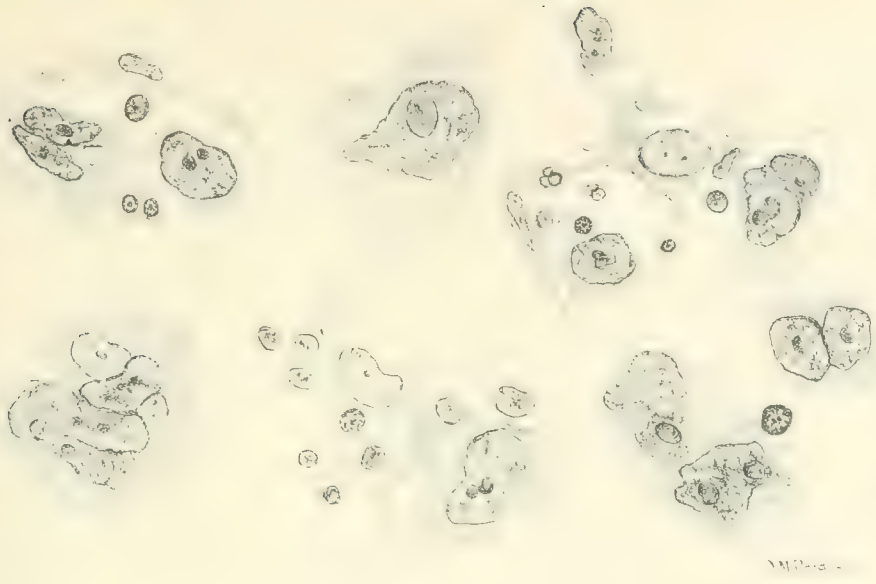

FIG. 5.

DIABETES INSIPIDUS, WITH A REPORT OF FIVE CASES.

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(From the Clinic of Prof. William Osler.)

In 1674, Thomas Willis,[1] physician to Charles II. of England, first recognized a distinction between two forms of diabetes, a saccharine and a non-saccharine. The literature on both diabetes mellitus and diabetes insipidus has grown to enormous dimensions, although the latter has not occupied the attention of clinicians to the same extent as the former. Particularly is this the case in this country, where indeed the literature on the subject is very meagre.

Definition.—Diabetes insipidus is a chronic affection characterized by the passage of large quantities of pale-colored, non-saccharine urine, having a low specific gravity and not containing albumin or casts.

Synonyms.—Among the numerous synonyms used for diabetes insipidus, many of which are misleading and incorrectly applied, the following are the commonest—polyuria, polyuria simplex, essential polyuria, diabetes spurious, habitual diuresis, hyperuresis, polydipsia, hydruria, azoturia and anazoturia.

Classification.—The last three names were suggested in 1838 by Robert Willis,[2] who first proposed the following classification of the cases of diabetes insipidus according to the amount of solids—particularly urea—present in the urine:—(1) Hydruria, under which were included those cases in which only the watery constituents of the urine were increased, whereas the daily excretion of urea remained normal. (2) Azoturia, distinguished by a marked increase both in the water and in the urea excretion. (3) Anazoturia, in which the water was increased but in which there was a marked deficiency in the urea elimination. Vogel and Lecorché made somewhat analogous classifications on a similar

basis. According to Strauss and Senator these classifications are superfluous. The latter holds that the various forms do not represent independent diseased processes, but merely various stages of one and the same disease, the amount of the urea excreted being dependent on the character of the food ingested and on the condition of the digestive tract.

The physiology of polyuria.—A transitory polyuria can be produced in the healthy organism under the following circumstances:

1. Conditions which increase the general blood pressure heighten the blood pressure in the renal arteries, with a consequent increase in the urinary excretion.

2. The entrance into the circulating blood of substance possessing high endosmetic equivalents causes an abundant passage of fluids from the tissue into the blood-vessels. This leads to an increase in the total volume of blood, with a resulting increased blood pressure and a constant polyuria.

3. A polyuria may be produced by the ingestion of substances which act as diuretics by mildly stimulating the glomerular epithelium to increased activity.

4. Psychical emotions may lead to a transitory polyuria. The duration of the polyuria depends on the grade of the excitement. Severe emotional excitement has frequently been the cause of a persistent polyuria.

A clear understanding of the manifold ways in which diabetes insipidus may be caused by lesions of various parts of the nervous system, may possibly be obtained by a brief review of the results that experimental physiology have added to our knowledge of urine excretion. Claude Bernard [3] did pioneer work in this direction and his results, which have been in part modified, may be summarized as follows:

1. Stimulation of the vagus in dogs has no effect on the color of the renal veins nor on the secretion of the urine. In rabbits, on the other hand, three notable results follow, viz., a dilatation and increased redness of the renal veins, and an increase in the urinary secretion.

2. Section of the greater splanchnic nerve causes, in dogs, an immediate increase in the amount of urine secreted. This increased functional activity can be stopped by stimulating the peripheral end of the cut splanchnic with the galvanic current. In

rabbits, section of the greater splanchnic causes the renal veins to contract and assume a darker red color. Stimulation of the peripheral end of the cut nerve had no result.

3. In rabbits at least, experimentation on one of the splanchnics influences only one kidney, viz., the one on the same side, whilst each of the vagi were found to influence both kidneys.

4. The splanchnics and vagi are antagonistic in their action on the renal vessels in rabbits.

Bernard's conclusions, although not confirmed in every detail by subsequent experiments, really formed the foundation for all future work. The researches of Eckhard,[4] of Giessen (for the most part confirmatory while demonstrating some errors), have added much to our knowledge concerning the effects of nervous influences on urinary secretion and have filled up many previously existing gaps. His results embrace practically all that we know at present on this point and may be summarized as follows:

1. Wounds of the floor of the 4th ventricle frequently produce polyuria, but the lesions do not always involve the point already pointed out by Bernard. In rabbits, at least, there is no definite point in the floor of the 4th ventricle injury of which will constantly produce a pure "hydruria."

2. The vagus has absolutely no influence on the secretion of urine in dogs or rabbits.

3. Cutting of the greater splanchnic nerve in dogs produces an immediate increase in the urinary secretion, the amount being about four times that normally eliminated. Stimulation of the peripheral end of the cut splanchnic stops the increased elimination. The greater splanchnic is therefore both the vasomotor and special secretory nerve of the kidneys in dogs. In rabbits, the splanchnics have absolutely no influence on the urine secretion.

4. In dogs, each splanchnic supplies branches to only one kidney, viz., to the one on the corresponding side, and, after cutting the nerve more urine is secreted only by that kidney which is on the same side as the cut nerve.

5. All other macroscopically recognizable sympathetic nerves, going to the kidney as well as their anastomoses with the phrenic, vagus and hypogastric nerves have no influence on the urine secretion.

6. Only the highest thoracic sympathetic ganglion and those

fine nerve fibrils which pass in the thoracic cavity to the aorta and surround it as well as other arteries including those of the kidney as a fine net-work, appear to influence the urine elimination. These nerves, however, are so fine that their influence cannot be determined by acting on them directly, so that conclusions regarding their action can only be obtained by eliminating their function through section of the spinal cord.

7. Section of the spinal cord at the level of the VI-VII cervical vertebrae (and also at higher levels) produces without exception an immediate and persistent suppression of the urine. Sections below this level give less certain and less prompt results, whereas sections of the cord below the XII dorsal vertebra have practically no effect whatever.

8. The diminished urine secretion following section of the cord is not the result of diminished blood pressure.

9. From the results of section of the cord at the above indicated level, it is apparent that the centre regulating the urine secretion is above this point; from the effect of medullary puncture it is quite certain that the centre is in the medulla or higher up.

10. It may be concluded then that the nerve fibres supplying the kidneys pass from the medulla in the spinal cord to the level of the VI-VII cervical vertebrae where they leave the cord in the uppermost thoracic nerves, whence they pass along the walls of the aorta and renal arteries to the kidneys.

11. There are a few poisons which produce a polyuria similar to that following Bernard's medullary puncture; among such poisons are curare and carbon monoxide.

12. In addition to Bernard's centre there are other areas of the brain, injury of which produces a temporary polyuria. Eckhard demonstrated that temporary polyuria followed:

a. After mechanical injury of the middle lobe of the cerebellum, in which, as he emphasizes, the blood pressure remains uninfluenced. The polyuria is most readily produced by injury of the posterior of the cerebellar convolutions visible from above. To this convolution Eckhard suggested the name "lobus hydruricus and diabeticus"; diabeticus because the polyuria was frequently accompanied by glycosuria.

b. After chemical irritation of the same point with chloride of iron, acetic acid, caustic potash or silver nitrate.

c. After electrical irritation of the same.

d. After injury of the posterior lobe of the rabbit's brain (the lobe which lies in the concavity of the temporal bone); the wound requiring to be comparatively deep, however.

The results under section 12 were obtained only with rabbits, the experiments being entirely negative with dogs.

Külz demonstrated that, in dogs, an increased elimination of urine followed intravenous injection of solution of urea, sodium nitrate, and 1% sodium chloride.

The importance of the above experiments is diminished from the fact that the results were obtained for dogs and rabbits alone and because the polyuria was merely transitory, lasting from a few hours to a few days.

It may be mentioned here that Claude Bernard discovered his so-called diabetic centre in 1849. This point is situated in the floor of the fourth ventricle between the centres of the pneumogastric and auditory nerves. Lesions of this centre in the dog caused a polyuria with the presence of glucose in the urine. Puncture at a point a little lower caused simple polyuria, while punctures at a point a trifle higher in the frontal direction, caused albuminuria.

Kahler, in experimenting on rabbits, was able to produce a permanent polyuria closely resembling diabetes insipidus in man. By injecting minute quantities of concentrated silver nitrate into various parts of the brain, he could cause a polyuria accompanied by polydipsia, both lasting several weeks. Microscopical examination of the involved brain areas were afterwards made in order to determine exactly the localization and extent of the lesion.

Kahler's results cited by Stoermer [5] are as follows:

1. One can produce a persistent polyuria in rabbits by destruction of minute areas of the cerebellum and medulla oblongata.

2. Whereas injury of the middle lobe of the cerebellum produces a more or less temporary polyuria, wounds of the medulla oblongata on the other hand are followed by a permanent polyuria.

3. The corpus trapezoides and the lateral part of the exposed portion of the medulla oblongata are the areas, injury of which is most likely to produce a permanent polyuria.

4. Destruction of the inner part of the cerebellum with Dieter's nucleus and the adjacent parts of the crura cerebelli causes practically always a permanent polyuria.

5. Experimentally produced permanent polyuria must be regarded as an irritation phenomenon.

6. The portions of the rabbit's brain designated in section 3 correspond in the human brain with the facialis-abducens region of the pons. One would look for a persistent polyuria in human beings when the lateral portion of the distal part of the pons and the proximal portion of the medulla are involved in some lesion.

Eckhard was led to conclude from his investigation, that the secretory function of the kidney was largely dependent on the action of specific secretory nerves and only in a very subordinate degree on the blood pressure. The subsequent investigations of Heidenhain and Grützner demonstrated the incorrectness of this view and showed that the elimination of the urine was in a large measure dependent on the blood pressure. Most physiologists at the present time do not believe that there are special secretory nerves to the kidney in man, although the question is not quite settled.

Strauss,[6] after acknowledging the correctness of Ludwig's theory of urine secretion, states that two possibilities for an increased urine secretion in diabetes insipidus come under consideration. An increased urine secretion may be caused:

1. By an increase of the blood pressure in the glomeruli.

This may be either a purely local process, in which a hyperaemia of the kidney is produced by a relaxation of the walls of the large renal arteries, or the result of an increase of the general blood pressure arising from an increase in the total volume of blood. Senator holds that an increase in the general blood pressure cannot be considered as the cause of the increased urine elimination in diabetes insipidus. According to Shroeder, only in those cases of primary polydipsia which Romberg, Pribram and Worm-Muller consider the cause of the polyuria in certain instances, can an increased blood pressure be regarded as a factor in the etiology. As a result of the polydipsia large quantities of water are absorbed, thus increasing the total blood volume and consequently the blood pressure, the latter demonstrating its action on the kidneys by the increased urine secretion.

2. By changes in the composition of the blood which alter its endosmotic power.

Mosler suggested that there was some abnormal substance in

the blood which acted like grape-sugar in drawing fluids from the tissues, thus increasing the blood pressure and consequently also the urine secretion. He was led to this opinion by finding inosite or muscle-sugar in the urine of a patient suffering from diabetes insipidus. Strauss doubted very much whether the inosite played an active part in the etiology of the polyuria. Although he found it in two of his three cases of diabetes insipidus, yet he was inclined to believe that the drinking of such large quantities of water is the cause of the inosituria, rather than the reverse. To two healthy individuals he gave 10 liters of water in 24 hours, and to a third the same amount in 12 hours. The urine of all three patients contained between 1 and 2 grams of inosite in 24 hours and the urine of the third patient contained the largest amount. Scherer says that in these instances we have a good example of a substance, inosite, which under ordinary circumstances, is broken up into CO_2 and H_2O, but which is washed out of the tissues and in part at least is excreted unchanged in the urine, when the tissues are suddenly flooded with large quantities of water.

Frequency.—Diabetes insipidus belongs to the rarer of the medical diseases. Up to March 10, 1902, the date on which Case V, the last of the hospital cases, was admitted there had been only 4 cases of the disease out of a total of 356,637 cases treated in the dispensary and wards of the Johns Hopkins Hospital, or only 0.001 per cent. During the same time, a period of twelve years, 170 cases of diabetes mellitus came under treatment. Statistics would seem to show that the disease was more common in Europe. Among 113,600 patients treated at the Charité, Berlin, from 1877 to 1896, there were 55 cases or 0.048 per cent. Eichorst observed 7 cases (or 0.02 per cent) among a total of 35,942 patients at the Zürich Hospital.

Etiology.—Diabetes insipidus is commonest in young persons. Of 85 cases analysed by Strauss[7] 9 were under five years of age; 12 between five and ten; 36 between ten and twenty-five; 21 between twenty-five and forty; and 7 between forty and sixty. In the statistics collected by Roberts, van der Heijden and Stoermer the largest number of cases occurred between 20 and 30 years of age. Gerhardt[8] states that more than half of all the cases occur between the tenth and fortieth years. Trousseau claimed that it was not unusual to find patients suffering from diabetes insipidus

whose parents were either glycosuric or albuminuric. Ralfe[9] emphasized the frequency with which a history of tuberculosis, syphilis and gout was obtained in one or both parents. He also held that malnutrition was a very important predisposing factor in the etiology of the disease in children.

Heredity is an important factor in a certain percentage of cases. Lacombe[10] reported an instance where 8 members of a family (5 males and 3 females) suffered from the disease in two generations. In Gabriel Pain's[11] case 7 members (5 males and 2 females) had diabetes insipidus in three generations. S. Gee[12] cites an instance in which 11 persons (9 males and 2 females) in four generations were affected. The most remarkable case in the literature, however, is that reported by A. Weil.[13] Of 91 members in four generations, 23 had persistent polyuria without any deterioration of health, namely, the great grandfather, 3 children, 7 grandchildren, and 12 great-grandchildren. Of the 22 affected descendents 11 were males and 11 were females. Exclusive of Weil's cases it would appear that the male are more prone to the disease than the female descendents. Weil believed that the cases in the family reported by him represented a special form of the disease, characterized by its heredity, also by a marked intensity of some of the symptoms, namely, a great dilatation of the bladder with the passage of enormous quantities of urine at each act of micturition. His cases were also characterized by an abnormally low specific gravity of the urine (the average being between 1001 and 1003 and maximum 1005) and the persistence of the disease from the cradle to the grave without its affecting the general health.

Clinical types of diabetes insipidus.—Two forms of the disease are generally recognized according to the etiology.

1. *Primary or idiopathic cases.*—This group includes the cases in which there is no physical basis for the disease: the great majority of the hereditary cases; as a general rule also, but probably with less right, the cases following exposure to cold, sun-stroke, alcoholic excesses, and infectious diseases are included in this division.

2. *Secondary or symptomatic cases.*—These include the cases with evidence of organic disease of the brain. Gerhardt includes in this group also those instances where the disease occurs in psy-

choses and in hysteria or neurasthenia. He states that it is very difficult to draw a definite line between certain cases in the two groups.

Stoermer, in his excellent monograph on diabetes insipidus, classified the cases according to their etiology under the following groups:

1. Diseases of the central and sympathetic nervous systems where actual anatomical changes occur.

Under this heading belong those cases of diabetes insipidus occurring—

a. After trauma.

b. After diseases of the brain and spinal cord, such as after brain tumors, apoplexy, syphilis, hydrocephalus, progressive paralysis and other diseases of the mind; also after bulbar disease and diffuse diseases of the cord.

c. After diseases of the cranial bones and vertebrae, and of the meninges. Under the latter would come the cases following meningitis cerebralis and epidemic cerebro-spinal meningitis.

d. After diseases of individual nerves, such as results from the pressure of an aneurism and disease of the ear.

e. After disease of the sympathetic nerves and ganglia, including the cases occurring at the end of intestinal disease and after Basedow's disease.

2. Diseases of the cerebro-spinal and sympathetic nervous system without appreciable anatomical changes.

Under this heading come those cases which may originate as a result of the following influences:

a. Psychical derangements.

b. Acute and chronic alcoholism.

c. Epilepsy and hysteria.

d. Inherited and psychical neuropathic characteristics.

3. General injury to health, as from excessive bodily and mental activity. Effect of intense heat, poor nourishment and particularly catching cold.

4. Infectious diseases—diphtheria, measles, scarlet fever, intermittent, typhoid and typhus fevers.

5. Cases without any discoverable cause whatever.

Traumatism involving some part of the nervous system is the attributable cause of the disease in a number of cases. Stoermer

claims that statistics show that about 30 per cent of all cases are traceable to injuries of the brain alone, as a result of traumatism. The essential factor in these trauma cases appears to be the involvement of the brain substance. Simple injury of the soft parts and bones does not appear to be sufficient to cause the disease. The only published case of diabetes insipidus following trauma, without loss of consciousness or other evidences of cerebral involvement, is reported by Nothnagel.[14] The patient was kicked in the abdomen and fell backwards, striking his head on the ground. The polyuria in such a case could quite readily be attributed to injury to the splanchnic or the sympathetic ganglia. There seems to be no definite relationship between the severity of the trauma symptoms and the grade or duration of the polyuria. Further, the disease does not appear to be confined to or to be commoner after injury to any special part of the brain. The polyuria is believed to be due to the effects of the concussion the brain sustains.

The disease may be caused by *cerebral tumors*. The nature of the tumor appears to be a minor factor. It may be a gumma, tuberculous focus, carcinoma, etc. The situation, however, is of greater significance. Diabetes insipidus occurs most frequently in association with tumors, which involve the floor of the fourth ventricle or which are situated in the immediate vicinity. Many such cases have been reported. On the other hand, tumors frequently occur in this situation without producing a diabetes insipidus.

Cerebral haemorrhages are said to be next in importance to tumors as factors in the etiology of diabetes insipidus. In 1865, Leyden[15] reported a case which followed cerebral apoplexy and Ollivier,[16] at a subsequent date, called attention to the frequency of such cases.

Just as in diabetes mellitus, so in diabetes insipidus, *syphilis* is believed to be the fundamental cause in a certain percentage of cases. It seems probable that it is the cause in a larger number of instances than is generally supposed. From the similarity of the symptoms in Cases II and IV to various published cases in which syphilitic brain lesions were found at autopsy, there is strong reason to believe that syphilis was the probable etiological factor, although both patients denied luetic infection and there was no outward manifestation of the disease.

Polyuria and polydipsia have long been described as symptoms

of cerebral syphilis. Fournier reported six cases in which these symptoms were present in association with various cerebral manifestations of the disease. Lancereaux, Oppenheim and others have also noted the association. The lesion has usually been found to be a syphilitic basilar meningitis. This was the lesion in Buttersack's case in which the disease was localized mainly in the interpeduncular space. Polyuria was the initial symptom in his patient. Nonne[17] states that it is not necessary, as was formerly held, that the lesion should involve the medulla oblongata or its vicinity. He asserts that all we can say is that polyuria and polydipsia are most liable to occur in syphilitic brain lesions which manifest themselves in the form of diffuse basilar meningitis. Many of the cases of diabetes insipidus due to syphilitic basilar meningitis have been associated with bilateral hemianopsia. Oppenheim considers an oscillating form of hemianopsia or a "hemianopsia bitemporalis fugax" as characteristic of basilar lues. This symptom was present in Case II and was strikingly illustrated by Case V. He described three such cases. One of these had polyuria and polydipsia. Besides the hemianopsia there were other evidences of basilar meningitis in the form of a double oculomotor paralysis and anosmia.

The syphilitic lesion may be a gumma, involving some portion of the base of the brain particularly the floor of the fourth ventricle. Occasionally a basilar meningitis and a gumma may be associated as in Nonne's case.

The following is a brief extract of one of Nonne's[18] cases, which seems of special interest owing to the rather striking similarity between it and Case II. The diagnosis was "Meningitis luetica gummosa basalis; Encephalomalacia arteriosklerotica (Hemiparesis sinistra, Hemiparalysis dextra, Hemianopsia duplex, Polydipsia, etc.)."

The patient was a man 54 years of age. Ten weeks previous to admission he had received an accidental blow on the right side of the head which caused a temporary loss of memory and was followed the next day by headache and impaired vision. He was admitted to the hospital for an injury to the left ankle ten weeks later. He was found to have a general left-sided hemiparesis, a partial left-sided homonymous hemianopsia, the eye-grounds being normal. Three months later he again entered the hospital com-

plaining of dizziness, attacks of unconsciousness and more marked impairment of vision. At this time he had intense thirst, drinking 8 or 10 litres of water daily. It was found on this admission that the patient had been treated for syphilis 30 years previously. He consequently was started on mercury and potassium iodide. After an interval of six months he again returned with markedly impaired vision, and it was found that he now had a double optic atrophy. The polydipsia and polyuria were now much less marked. Three weeks later he was a fourth time admitted to the hospital for a right-sided hemiplegia and a motor aphasia. He was now drinking about four or five litres of fluid and voiding about the same amount of urine. Three months later the patient died and the following brain lesions were found: The pia was thickened in the vicinity of the optic chiasma. There was also a gumma infiltrating the right optic tract and invading the right internal capsule as well as the left optic thalamus. A focus of softening, the size of a walnut, was present in the left hemisphere. This partially involved the left internal capsule. The microscopic examination of the tumor showed that it was a gumma. There was marked arteriosclerosis of the basilar vessels and those of the tumor showed marked proliferating endarteritis.

Considering the fact that, from the history he gave, Case II must have had hemianopsia, these two cases were very similar.

Heijden[19] reported a case in which the disease was attributed to an existing *chronic hydrocephalus.*

A few cases of diabetes insipidus have been associated with various mental diseases as *progressive paralysis* of the insane, imbecility and mania. Landouzy and Ebstein have observed the association of the disease with the latter two mental affections.

Diseases involving the *spinal cord* have in rare instances been regarded as the cause of the diabetes insipidus. Thus, Schlesinger[20] met it in a patient with tabes dorsalis. He, however, suggests the possibility of the diabetes being caused by silver nitrate, which had been administered to the patient. In a case of Westphal's the disease occurred in association with spastic spinal paralysis. In this instance sugar was present in the urine at first, but afterward disappeared. F. Schultze saw the disease in a patient with complicated nervous symptoms due to a diffuse tumor involving the cord. Instances of persistent polyuria have been ob-

served by Krauss in syringo-myelia and by Friedrich in hereditary ataxia.

In some instances the disease has been attributed to an existing *meningitis.* In the majority of cases the meningitis has been found most marked in the region of the medulla and base of the brain. Such cases are comparatively numerous in the literature. In this connection may also be mentioned the cases of diabetes insipidus which have followed *inflammation of the middle ear.* Strauss was one of the first to draw attention to this association. He held that the inflammation of the middle ear extended so as to involve the meninges and brain substance, thus disturbing the normal cerebral functions. In a case reported by J. S. Jewell, of Chicago, the urine diminished when the pus discharged and with the subsidence of the ear affection the polyuria ceased. Jewell believed, however, that the diabetes insipidus in such cases is probably caused by a reflex irritation of Bernard's centre, from involvement of the auricular branch of the vagus in the diseased ear, and also from involvement of a branch of the glosso-pharyngeal. Similar cases are reported by Kien and Kiener.

As further instances in which the diabetes insipidus has been attributed to reflex action from stimulation of certain peripheral nerves, may be mentioned the cases of Hadra and Ralfe in which the disease was associated with *aneurysms of the carotid and aorta* respectively. Here probably the reflex stimulus was conveyed by branches of the vagus.

The sympathetic plays the most important rôle among the peripheral nerves in the etiology of diabetes insipidus. The influence which *diseases of the abdominal organs* as well as that of distant portions of the nervous system may have on the renal functions is clearly shown by Ralfe's account of the course of the nerves forming the renal plexus, which is as follows: "It is interesting to trace the course of the nerves forming the renal plexus, as irritation from eccentric or distant sources may play a part in inhibiting the renal nerves. Thus, the nerves forming the renal plexus are derived chiefly from the solar plexus; as the right vagus and great and lesser splanchnics join the solar plexus, it is probable that branches of these nerves enter the kidney by way of the renal plexus. The splanchnics also send branches direct to the renal plexus; and the left vagus sends some fibres to the left kidney.

They contain medullated and non-medullated fibres; and Krause has traced the latter as far as the apices of the papillae. Their mode of termination is unknown. Physiologically vaso-constrictor, vaso-dilator, and sensory fibres have been ascertained. The connection through the vagus brings us into range with the medulla oblongata, and with many organs susceptible of tubercular or syphilitic growths, or of sudden shock, such as chill. The solar plexus may propagate the effect of abdominal new growths or aneurysms." As early as 1794, Frank observed a fatal case of diabetes in *disease of the intestine.* Schapiro[21] observed five cases of diabetes insipidus in Eichwald's clinic, in St. Petersburg, in which disease of the intestine was regarded as the cause. Autopsies were obtained on two of the cases. There was found an increase of the connective tissue, atrophy of the ganglion cells and dilatation of the vessels of the semi-lunar ganglia, and extensive fatty degeneration and destruction of the axis cylinders of the greater splanchnic. The kidneys were hypertrophied, hyperaemic and their afferentia markedly dilated; the small and large intestine showed signs of an old catarrh and numerous irregular ulcers.

Dickinson reported a case of diabetes insipidus in a patient with *carcinoma of the liver and involvement of the solar plexus.* At the autopsy it was found that there were carcinomatous metasteses in the retroperitoneal lymph-glands which involved branches of the solar plexus. There was also a marked hyperaemia of the kidneys.

Severe shock and fright have been followed by diabetes insipidus. Here the disease is considered by most observers to be caused by a paralysis of the vasomotor centre in the medulla.

Polyuria is not an uncommon symptom in *hysteria, epilepsy, tetanus and chorea,* and it reaches such a grade and has been so persistent in some instances that many observers have been inclined to consider them cases of true diabetes insipidus. Such instances have been observed by Oppolzer, Kien, Buttersack, Külz and others.

From the foregoing it will be seen that apparently a large number of etiological factors enter into the causation of diabetes insipidus. Whether the case belongs to the idiopathic or the symptomatic group it matters not. The determining factor is a disturbance of the secretory function of the kidneys. Gerhardt[22]

says that in idiopathic diabetes "the disease is due to a disturbance of the secretory function of the kidneys and not to an increase in the thirst or to blood changes." He draws an analogy between the polyuria in this disease and the hypersecretion of the gastric juice in functional disturbances of the stomach. Osler[23] says, "It is doubtless of nervous origin. The most reasonable view is that it results from a vaso-motor disturbance of the renal vessels, due either to local irritation, as in a case of abdominal tumor, to cerebral disturbance in cases of brain lesion, or to functional irritation of the centre in the medulla, giving rise to continuous renal congestion."

Symptoms. 1. *Polyuria.*—The increase in the amount of urine eliminated is the most characteristic and constant symptom of the disease. The quantity voided may be enormous, reaching as high as from 20, 30 to even 40 litres in the 24 hours. Trousseau (24) had a patient 24 years of age who passed 43 litres in a day. In a few instances the weight of the urine voided daily practically equalled the weight of the patient. Van der Heijden reports an instance of a girl 6 years of age and weighing 19½ pounds who passed daily from 14½ to 19½ pounds of urine, and Vierordt cites an instance of a child weighing 13.2 kilogrammes, voiding 12.3 kilogrammes of urine daily. The amount of urine passed at an individual voiding is occasionally enormous. Thus in Case II, reported below, the patient voided 1700 cc. at one time in my presence. The urine, as already stated, is extremely pale, often with no more color than water, of a faintly acid reaction, and of low specific gravity, the latter ranging usually between 1000 and 1005. It is to be remembered, however, that where the urea elmination is high the specific gravity of the urine may remain practically normal. Thus Laparguois observed a case in which 6 litres of urine were passed with a specific gravity of 1017. The urine is practically always free from albumin, sugar and casts. Comparative investigation made by Neuschler[25] and Falck[26] showed that after the drinking of large quantities of fluid, the healthy individual shows an earlier and more rapid increase in the amount of urine. In the diabetic patient, however, the increase lasts much longer and in the later hours the amount surpasses that voided by the healthy person. Neuschler considers this slow absorption a characteristic

feature of diabetes insipidus. On the other hand, the restriction of liquids fails for a much longer time to cause any diminution in the amount of urine voided by the diabetic patient than by the healthy person. These results have been confirmed by others and most recently by Strubell.[27]

The question as to whether a patient passes more urine than he drinks of fluids has been a much debated one. The majority of observers hold that it is impossible for a patient's urine to remain in excess of the fluids ingested for any length of time, and claim that where such observations have been reported they are inaccurate. It seems reasonable that, during the first few days of the disease at least, the urine could exceed the fluids ingested, owing to fluids being extracted from the tissues. In considering the excess of urine over fluids one has to keep in mind the fact that the solid food contains a considerable percentage of water. Notwithstanding this fact, the excess of urine is occasionally so large that it could not be accounted for in this way. Thus in Case II where all the fluids (including those taken with the meals) were carefully measured, the urine for days exceeded the fluids by from 400 to 6355 cc. (see table). This seems more extraordinary when it is considered that the patient gained $18\frac{3}{4}$ pounds during this time. It has been thought by some that the patients absorb moisture from the air. Jepson[28] is authority for the statement (which I have not been able to confirm) that Dickinson found that one patient, between the acts of micturition (no food or drink being taken), gained respectively: $15\frac{1}{2}$ ounces in weight in 3 hours, $19\frac{3}{4}$ ounces in 5 hours. I know of no observation confirming these results. As a general rule more urine is voided during the night than during the day. This was well illustrated in Case III.

The following statements may be made regarding the constituents of the urine:

a. The *urea* is usually excreted in normal amount. Occasionally it is enormously increased, reaching as high as 70 to 80 grammes daily. These constitute the cases of azoturia of the older writers. In no case has the increased nitrogen output in diabetes insipidus been definitely shown to be due to increased nitrogenous destruction of the tissues. Where it is increased it is practically always dependent on the increased ingestion of albumin as a result of the enormous appetite present in some cases. Not infrequently the urea is diminished.

b. The *sodium chloride* is usually about normal but occasionally it is markedly increased. In Cases I and II the highest daily amounts were 17.25 and 16.35 grammes respectively.

c. There are but few recorded estimations of the *uric acid* and *kreatinin.* Those published indicate that they are within normal limits. In Case I the uric acid was usually at the lower limit for normal.

d. The *phosphoric acid* excretion varies. It is usually about normal. In this connection may be mentioned Tessier's phosphatic diabetes, in which there is a marked increase in the P_2O_5 excretion. Cases in which the excretion has reached as high as 6.6 grammes in the 24 hours have been reported. Generally there is no phosphaturia.

e. Albumin is not present, an important point in differentiating the disease from chronic interstitial nephritis.

f. Sugar is absent. It may be mentioned here, however, that a few cases of diabetes insipidus have been reported where the disease has passed into true diabetes mellitus. The reverse has also been observed. The cases in which these transitions have occurred have been chiefly those with traumatic injuries to the brain.

g. Inosite has occasionally been found in the urine. It has no practical importance in the disease. Its occurrence in the urine is believed to be due to the washing out of the inosite from the muscular tissues by the enormous amounts of fluid drunk. It has been found in the urine of healthy persons after they have taken large amounts of water to drink.

2. *Thirst* is practically a constant symptom. Indeed it is said in the majority of instances to be the first symptom the patient complains of. The question as to whether in diabetes insipidus the polyuria or the polydipsia is primary has been a much debated one. The majority of observers, including the more recent ones, incline to the view that polydipsia is primary. Nothnagel's [29] case is usually cited as a typical instance of a primary polydipsia. The patient, a man 35 years of age, was kicked in the abdomen and fell striking his head in the region of the right ear against a stick of wood. He was not rendered unconscious but was made quite dizzy. Half an hour after the blow the patient began to have intense thirst and drank three litres of water and it was not

until about three hours later that the first urine was voided. In many cases, however, it is difficult to determine which is primary. The thirst is sometimes intense. Dr. Osler's patient (Case V) stated that he practically lived to drink. In more than one case, where the patient has been confined in a room and cut off from liquids in order to ascertain the effect on the urine elimination, he has drunk his own urine.

Strubell's[30] experience with one of his patients illustrates well the intense agony suffered from the thirst in these cases and also the difficulty, even when the patient is guarded by force, to carry out accurate tests in determining the effect of restriction of liquids on the urine elimination. Strubell confined his patient in an attic room with barred windows so that there was apparently no chance of his securing any fluids. On one occasion the man drank 1400 cc. of his own urine during the night. On a second occasion he was caught in the act of collecting rain-water in a drinking cup from the eaves of the roof. He had secured half a litre in this way. On a third occasion, this being the last day of the experiment, his thirst became so intense that he wrenched the iron-bars from the window, climbed on to the roof and entered another room through a barred window and was caught while assuaging his thirst at a water-tap.

The *amount* of fluids taken may reach the enormous total of 50 litres daily and it is not unusual for the patient to drink a quart or more at one draught. Buttersack gives the following conditions as indicating a primary polydipsia in any particular case: (1) There is normal sweat secretion. (2) The urine is less than the amount of fluids. (3) The polyuria ceases on cutting off the fluids drunk. (4) The urine elimination and the amount of liquids taken run parallel. Stoermer gives practically these same points, and states further that in primary polyuria the blood is more concentrated than normal, whereas in primary polydipsia there is no change.

3. *Absence of sweating* is the customary rule. A very few cases have been recorded where sweating has been associated with the polyuria. The insensible perspiration is also diminished. This has been confirmed by the researches of Strauss, Flatten and Strubell. The formula for determining the insensible perspiration during a given period is as follows:

(Weight at the beginning + intake) — (weight at the end + output) = Insensible perspiration.

The *insensible perspiration* has been found to be about half that in a normal individual. Compared with the amount of urine voided it is enormously reduced.

4. The appetite varies greatly. In the majority of cases it is very poor, and is often complained of by the patient. Nausea and vomiting frequently occur. Occasionally the appetite is enormous as in Trousseau's case, in which the restaurant-keeper paid the customer to remain away. These cases probably constitute the so-called azoturia cases, the increase in the urea being due to the extraordinary amount of nitrogenous food eaten.

5. *Constipation* is the rule. This is due to the absorption of fluids from the intestinal tract.

6. *The blood* shows but little change. Strauss and Stoermer found the specific gravity increased. The blood count varies but little from the normal.

7. *The eyes* are apparently subject to changes. Cataract has been described by various observers. This has been attributed to the extraction of water from the lens. I have found no reference to the occurrence of xanthomata on the eyelids. It is, therefore, of interest that large xanthoma plaques were present on both upper eyelids in *Case I.* In cases where the disease is due to some brain lesion choked-discs may be found.

8. *Headache* is often a very distressing symptom even in cases without definite evidences of brain disease. It was a prominent symptom in *Cases II and IV*, and was present early in *Cases III and V.* Occasionally there are severe pains in the lumbar region and in the legs early in the disease.

9. The sexual functions are frequently disturbed and impotence occasionally develops. The latter sometimes disappears with the improvement of the patient's condition.

10. *Loss in weight* occurs frequently at the onset but one rarely sees the grade of emaciation observed in diabetes mellitus excepting in some of the symptomatic cases.

11. Notwithstanding the extraordinary disturbance of the urinary secretion in diabetes insipidus, there appears to be no very marked change in the *metabolic functions.* The nitrogen metabolism has not been very carefully studied. It was followed in

Case I. The nitrogen intake and output were carefully estimated. The case was studied in two periods. During the first period of 9 days, during which time the patient took no medicine, it will be seen from the nitrogen-balance tables that the body took on 34.8279 grammes of N. or an average of 3.8697 grammes daily. During the second period, the patient was given two grains of zinc valerianate three times a day in order to ascertain whether there was any change in the metabolism. During this period of 9 days only 14.9478 grammes or a daily average of 1.6608 grammes were added to the organism. The extraordinary and rather paradoxical feature in the case was that notwithstanding the fact that in 18 days the patient added 49.7757 grammes to his organism, he lost 200 grammes or about one-half a pound in weight. The only other observations regarding the nitrogen intake and output I have been able to find have been those of Strubell and Vannini. Strubell found in one case that 0.54 grammes were added to the body daily for 8 days and in another 1 gramme was lost daily for 5 days. In one of Vannini's cases 1.1 grammes were added daily for 6 days and in another 2.955 grammes were lost daily for 4 days. No definite references are made to the patient's weights in these cases.

12. *Oedema* of the feet is a rare symptom, but has been described. It usually occurs in the late stages of the disease in the asthenic emaciated cases. There was a history of it in Cases I and II.

13. I find practically no reference to the condition of the *knee-jerks* in this disease. It is interesting that they were exaggerated in 4 of the 5 cases here reported, and markedly so in 2 of them.

Prognosis.—The course of the disease is entirely dependent upon the nature of the primary trouble. If it be due to some organic disease, involving the brain or the abdominal viscera, the patients are liable to lose weight and flesh rapidly, and for the general health to become markedly impaired. Death is more likely to occur within a few years after the onset of the symptoms in this class than in the essential or idiopathic cases. The duration of these cases is largely dependent upon whether certain vital structures are involved or not. In the idiopathic form of the disease the general health is rarely impaired to the same degree. The patients lose weight for a few weeks after the onset, but later they

retain their weight, and many of them look comparatively healthy and robust. Dr. Osler states that the affection has been known to persist for fifty years. Death usually results from some intercurrent disease. Occasionally a spontaneous cure may occur.

Diagnosis.—The disease may be simulated by chronic interstitial Bright's disease. The amount of urine in the latter rarely reaches the quantity voided in the former, and the presence of traces of albumin and a few hyaline casts settles the diagnosis. The absence of sugar excludes diabetes mellitus. The question as to whether the disease should be differentiated from a hysterical polyuria or not is a debatable one. In the majority of the monographs on diabetes insipidus the polyuria of hysteria is classified as one of the forms of the disease. Usually it is put in the symptomatic group. As a general rule the polyuria of hysteria is transitory, and there are usually nervous and physical phenomena present which render the cause of the polyuria clear. Some writers have attempted to classify those cases in which thirst is the first symptom as a separate and independent disease, applying the term primary polydipsia to this group, but the evidence in favor of such a classification does not at present seem to be sufficient.

Treatment.—The treatment is very unsatisfactory. It is useless to attempt to restrict the amount of fluids, for by doing so there is practically no permanent diminution in the polyuria and the general health is injured. Various sedatives have been used. Preparations of opium have been administered with benefit. The beneficial results are probably due to the lessening of the sense of thirst. The commonest sedative in use is valerian. Either the powdered root, given at first in 5-grain doses three times daily and increased until the patient takes as high as 2 drams daily, or the valerianate of zinc in 15-grain doses increased to 30 grains three times a day, may be administered. Ergot, bromides, salicylates and antipyrine have all been tried with varying and on the whole unsatisfactory results. Galvanization of the spine has been advocated. Adrenal extract has been used by W. F. Clark with improvement in the symptoms and was tried in Case I without any beneficial result.

There seems little doubt that some cases are due to syphilitic brain infection and in such instances potassium iodide or mercurial inunctions or both together should be given a thorough

trial. There is occasionally marked improvement in the patient's strength and weight, even though the amount of urine may not be specially diminished.

Case I. (General No. 21086.)

Diabetes Insipidus of doubtful etiology. Probably belonging to the idiopathic group. Disease of ten years' duration. Polydipsia the initial symptom. Bilateral xanthoma palpebrarum. Double suppurative otitis media. History of oedema of the feet. Study of metabolism showing marked excess of nitrogen intake over output with a slight loss in weight. Exaggerated knee-jerks.

A. S., male, aged 44, married, white, bar-keeper, was admitted to the Johns Hopkins Hospital, under Prof. Osler, on November 1, 1897, complaining of shortness of breath, weakness, intense thirst and the passing of large quantities of urine. There was nothing of special importance in the patient's family history. There was no hereditary history of any kind. Two of the patient's children, however, died in infancy of meningitis.

As a child the patient had measles. When a boy he had a fall, hitting his head. There were no after effects. As a boy and young man he says he was always strong and healthy. There is no history of typhoid fever, pneumonia, rheumatism or gout. Ten years ago he had what he describes as an attack of bilious remittent fever. During this attack he had no chills, but a rather high fever and an irritable skin eruption resembling hives. Three years ago he was operated on for fistula-in-ano. The fistula has never entirely healed. About this same time a purulent discharge made its appearance from the right ear, followed a week later by a similar discharge from the left ear. He attributed it to exposure to cold. For the last three years also he has noticed that his teeth have been getting loose and falling out. He has lost five in this way. Ever since the fistula operation he has been having several loose movements of the bowels daily until quite recently, when the diarrhoea ceased. For several years the patient was a bar-keeper, and drank from ten to twelve glasses of beer daily. More recently he has been a cigar-maker. He smokes moderately. Denies having had lues or gonorrhoea.

The patient dates his present illness from ten years ago with the

sudden onset of an insatiable thirst. He says that he would drink as much as four to five gallons of fluid a day, and that it was not unusual to drink as much as a quart at a draft. With the consumption of water he noticed that he was passing equally large amounts of pale, almost colorless urine. He asserts that the amount of urine passed was greatest in the first year of his trouble. Sometimes he would void as much as "a pailful" during the night. His appetite has never been inordinate, and he has had no gastric symptoms. His skin has always been dry, and he never perspires even in the warmest weather. He states that he had an "eczema on the head" one year ago. Seven years ago he first noticed some swelling of the feet. This would appear at intervals of from two weeks up to four months until three years ago, since which date he has been entirely free from oedema. Three years ago he began to complain of shortness of breath on exertion. This has been persistent and has gradually increased. For four years he has noticed that his strength has been decidedly less, but he has continued at work up to the present. There have been no special motor disturbances. He states that his arms and legs frequently "go to sleep," but otherwise he has had no sensory disturbances. He has never suffered from headaches nor from body pains. His eyesight has always been good until three months ago; since then he has been unable to read print as well as formerly. At the onset of his illness ten years ago his weight was 230 pounds. During the first year he lost thirty pounds, and since then thirty pounds more, his present weight being about 170 pounds. He suffers from cough practically every winter, and states that he has been treated for emphysema. He thinks that his thirst and polyuria have been perceptibly diminishing in recent years.

Physical Examination.—The patient is a rather unusually stout man, weighing on admission 177 pounds. His lips and mucous membranes are of good color; tongue coated with a heavy gray fur. His teeth are poor; several are absent and a number quite loose. On each upper eyelid there is a large flat xanthoma measuring 1.75 x .75 cm. His skin is dry.

He has a definite emphysematous chest. The breath sounds are everywhere feeble.

The point of maximum cardiac impulse is in the sixth interspace 11 cm. from the median line. The absolute cardiac dullness is

obliterated by the emphysematous lungs. There are no cardiac murmurs; the second pulmonic sound is relatively accentuated. The impression obtained from the examination of the heart is that it is appreciably enlarged. The border of the liver is distinctly felt 3 cm. below the costal margin in the mammillary line. The spleen is not palpable. The abdominal examination is otherwise normal. The examination of the genitalia is negative; no evidence of a scar on the penis. On examination of the anus there is a distinct scar, the result of the fistula operation. There is no thickening of the long bones; no general granular enlargement. The patellar, triceps and wrist reflexes are slightly exaggerated; no ankle-clonus. Cremasteric and epigastric reflexes are normal.

November 6, 1897.—Dr. Randolph reports that the fundi of the eyes are negative, but that there is a double suppurative otitis media.

November 16, Blood Examination.—Red blood corpuscles 5,960,000; leucocytes 9000; haemoglobin 96 per cent.

Bremer's and Williamson's diabetic blood tests are both negative.

February 3, 1898.—The patient's main complaint during his stay in the hospital has been dyspnoea, and precordial oppression on slightest exertion. He has not complained particularly of thirst. He has been permitted all the water he desires to drink. The medicinal treatment has been varied. In order to ascertain the effects of various drugs on the urine elimination, the patient has been given in succession for a few days valerianate of zinc, adrenal extract, codeia and tincture of ergot. There was no material diminution in the urine voided. The xanthomata have been excised for histological study. The patient is discharged to-day without any material change in his condition.

Urine Examination. November 2 to 3. Total amount 3260 cc.; very pale yellow, trifle cloudy, faintly acid, sp. gr. 1007; no sediment. There is no sugar, albumin, or casts. The uric acid was 0.2832 grammes, and the urea 24.45 grammes. During this same twenty-four hours 4895 cc. of liquids were drunk. The urine was examined daily during his entire stay in the hospital, and at no time were any albumin or casts found. The highest urea excretion on any one day was 43.12 grammes.

With the object of determining whether or not there were any

material changes in the metabolic functions in this case, a careful analysis of the ingesta and excreta was made during a period of 18 days, commencing on the morning of November 12. During the first 9 days the patient received no medicine. During the second 9 days he was given valerianate of zinc (2 grains three times daily) to see if the amount of urine would be diminished, and whether there would be any change in the nitrogen metabolism or in the various constituents of the urine.

The patient's weight at the commencement of the experiment was 177 lbs. or 80.4 kilogrammes. A normal individual of this weight should receive sufficient of the three food-stuffs to yield 2800 calories.

The patient received the following food daily during the period of 18 days:

Milk	1100 grammes
Ham (without fat)	200 "
Bread	250 "
Tea infusion	200 "

All the ice and lime water the patient required to quench his thirst was allowed him, and accurately measured.

The amount of albumin, fat and carbohydrates contained in the above diet with their caloric value is as follows:

Albumin	107.15 grms.	= 439.31 Calories.
Fat	50.37 "	= 468.44 "
Carbohydrates	180.90 "	= 741.69 "
		1649. + "

The method of separating the faeces of the two periods by the use of vegetable carbon was adopted.

The nitrogen determinations in the ingesta and excreta were made by the Kjeldahl Method. The uric acid was estimated by the Hopkins process; the alloxuric bodies and xanthin bases by the Arnstein Method; chlorides by the Volhard and Falck Method, modified by Arnold; the phosphoric acid by uranium nitrate method; and the urea by oxidation with sodium hypobromite and measuring the amount of evolved nitrogen gas.

PERIOD I. TABLE I.

NITROGEN INGESTED IN GRAMMES.

Date.	Day.	Ham.	Bread.	Milk.	Tea.	Total.
XI, 12–13	1	11.8329	3.5226	7.0080	0.0175	22.3810
XI, 13–14	2	11.8329	3.5226	6.7540	0.0175	22.1270
XI, 14–15	3	11.8329	3.5226	6.4460	0.0175	21.8190
XI, 15–16	4	11.8329	3.5226	6.6660	0.0175	22.0390
XI, 16–17	5	11.8329	3.5226	6.6220	0.0175	21.9950
XI, 17–18	6	10.9344	3.5226	6.6000	0.0175	21.0745
XI, 18–19	7	10.9344	3.5226	6.1380	0.0175	20.6125
XI, 19–20	8	10.9344	3.5226	6.4680	0.0175	20.9425
XI, 20–21	9	10.9344	3.5226	6.6660	0.0175	21.1405

PERIOD II. TABLE II.

NITROGEN INGESTED IN GRAMMES.

Date.	Day.	Ham.	Bread.	Milk.	Tea infusion.	Total.
November.						
.....21–22.....	1	10.9344	3.5226	6.4020	0.0175	20.8765
.....22–23.....	2	10.9344	3.5226	6.2140	0.0175	20.6885
.....23–24.....	3	10.9344	3.5226	7.2160	0.0175	21.6905
.....24–25.....	4	10.9344	3.5226	6.8200	0.0175	21.2945
.....25–26.....	5	8.3740	3.5226	6.9740	0.0175	18.8881
.....26–27.....	6	8.3740	3.5226	6.4120	0.0175	18.3261
.....27–28.....	7	8.3740	3.5226	6.3580	0.0175	18.2721
.....28–29.....	8	8.3740	3.5226	6.5120	0.0175	18.4261
.....29–30.....	9	8.3740	3.5226	5.8520	0.0175	17.7661

PERIOD I. TABLE III.

Date.	Day of observation.	Patient's weight.	Amount of urine in cc.	Reaction and specific gravity.	Total nitrogen in grammes.	Total alloxuric body nitrogen.	Uric acid.	Uric acid–nitrogen.	Xanthin bases nitrogen.	Chlorides.	Total Phosphoric acid.	Urea.	Remarks.
November													
12–13..... ...	1	177 lbs. 80 K. 400 G.	4,385	Acid 1.009	16.0491	..	0.5393	0.1797	..	11.6202	3.0061	37.27	
13–14.....	2	176 lbs. 80 K. 000 G.	5,670	Acid 1.009	20.1852	..	0.6095	0.2031	..	17.0100	3.5380	42.52	
14–15.....	3	177½ lbs. 80 K. 600 G.	5,750	Acid 1.008	17.4800	0.2530	0.5232	0.1744	0.0786	17.2500	2.7600	37.37	
15–16.....	4	178 lbs. 80 K. 900 G.	5,870	Acid 1.008	18.9014	0.3639	0.4872	0.1624	0.2015	14.3815	3.1111	41.09	
16–17.....	5	178 lbs. 80 K. 900 G.	5,330	Acid 1.006	17.2692	0.2505	0.2185	0.0728	0.1777	13.7920	2.6117	37.31	
17–18.....	6	177 lbs. 80 K. 400 G.	6,150	Acid 1.007	16.3590	0.2521	0.3751	0.1250	0.1271	15.7500	2.8905	36.90	
18–19.....	7	176½ lbs. 80 K. 600 G.	4,030	Acid 1.007	13.5408	0.2780	0.3425	0.1141	0.1639	8.0600	2.2105	30.22	
19–20.....	8	177 lbs. 80 K. 400 G.	3,790	Acid 1.006	13.8440	0.1023	0.1174	0.0391	0.0632	11.3700	2.4407	30.32	
20–21.....	9	176½ lbs. 80 K. 200 G.	6,140	Acid 1.006	18.1774	0.2763	0.3929	0.1309	0.1454	9.2100	2.1858	42.98	
Total.....	..	....	47,115	9.066	151.8061	1.7761	3.6056	1.2015	0.9574	118.4437	24.7544	335.98	
Average	..	....	5,235	1.0073	16.8673	0.2537	0.4006	0.1335	0.1367	13.1604	2.7504	37.33	

PERIOD II. TABLE IV.

Date.	Day of observation.	Patient's weight.	Amount of urine in cc.	Reaction and specific gravity.	Total nitrogen in grammes.	Total alloxuric body nitrogen.	Uric acid.	Uric acid-nitrogen.	Xanthin bases nitrogen.	Chlorides.	Total Phosphoric acid.	Urea.	Remarks.
November.													
.....21–22.....	1	176½ lbs. 80 K. 200 G.	5100	Acid 1.005	14.2800	0.1532	0.3570	0.1190	0.0342	8.6700	2.3460	30.60	
.....22–23.....	2	177½ lbs. 80 K. 600 G.	5295	Acid 1.005	17.3676	0.0847	0.1217	0.0405	0.0442	14.2965	2.5416	33.35	
.....23–24.....	3	177 lbs. 80 K. 600 G.	5520	Acid 1.008	18.2160	0.1545	0.4029	0.1343	0.0202	11.5920	2.9876	36.98	
.....24–25.....	4	175¾ lbs. 79 K. 800 G.	4280	Acid 1.009	17.2056	0.3980	0.3466	0.1155	0.2825	9.3160	2.6707	38.52	
.....25–26.....	5	177½ lbs. 80 K. 600 G.	5750	Acid 1.009	21.7350	....	0.3852	0.1284	....	12.2125	3.0475	43.12	
.....26–27.....	6		5460	Acid 1.008	17.6904	0.3003	0.4149	0.1383	0.1620	6.0980	2.7300	38.22	
.....27–28.....	7	175½ lbs. 79 K. 700 G.	6740	Acid 1.006	17.3892	0.3909	0.3211	0.1070	0.2839	13.4800	2.7903	33.70	
.....28–29.....	8	176½ lbs. 80 K. 200 G.	4460	Acid 1.008	16.6912	....	0.4950	0.1650	....	6.2440	2.2300	35.32	
.....29–30.....	9		5300	Acid 1.007	16.1120	0.3445	0.6148	0.2049	0.1396	7.4200	2.5440	34.45	
Total.....	..	...	47.905	9.065	156.6890	1.8261	3.4592	1.1529	0.9666	89.3290	23.8877	324.26	
Average.....	..	...	5.322	1.0072	17.4088	0.2608	0.3842	0.1281	0.1380	9.9254	2.6541	36.02	

PERIOD I. TABLE V.

NITROGEN BALANCE TABLE.

Date.	Day.	Nitrogen ingested.	Nitrogen excreted.			Balance.
			In urine.	In faeces.	Total.	
November.						
12–13.....	1	22.3810	16.0491	0.8330	16.8821	+ 5.4989
13–14.....	2	22.1270	20.1852	0.8330	21.0182	+ 1.1088
14–15.....	3	21.8190	17.4800	0.8330	18.3130	+ 3.5060
15–16.....	4	22.0390	18.9014	0.8330	19.7344	+ 2.3046
16–17.....	5	21.9950	17.2692	0.8330	18.1022	+ 3.8928
17–18.....	6	21.0745	16.3590	0.8330	17.1920	+ 3.8825
18–19.....	7	20.6125	13.5408	0.8330	14.3738	+ 6.2387
19–20.....	8	20.9425	13.8440	0.8330	14.6770	+ 6.2655
20–21.....	9	21.1405	18.1774	0.8330	19.0104	+ 2.1301
Total..... ..		194.1310	151.8061	7.4975	159.3031	+34.8279
Average		21.5701	16.8673	0.8330	17.7003	+ 3.8697

PERIOD II. TABLE VI.

NITROGEN BALANCE TABLE.

Date.	Day.	Nitrogen ingested.	Nitrogen excreted.			Balance.
			In urine.	In faeces.	Total.	
November.						
21–22.....	1	20.8765	14.2800	0.5213	14.8013	+ 6.0752
22–23.....	2	20.6885	17.3696	0.5213	17.8909	+ 2.7976
23–24.....	3	21.6905	18.2160	0.5213	18.7373	+ 2.9532
24–25.....	4	21.2945	17.2056	0.5213	17.7269	+ 3.5672
25–26.....	5	18.8881	21.7350	0.5213	22.2563	— 3.3682
26–27.....	6	18.3261	17.6904	0.5213	18.2117	+ 0.1144
27–28.....	7	18.2721	17.3892	0.5213	17.9105	+ 0.3616
28–29.....	8	18.4261	16.6912	0.5213	17.1125	+ 1.3136
29–30.....	9	17.7661	16.1120	0.5213	16.6333	+ 1.1328
Total..... ..		176.2285	156.6890	4.6919	161.2807	+14.9478
Average		19.5809	17.4088	0.5213	17.9200	+ 1.6608

Case II. (General No. 33393.)

Diabetes insipidus probably due to cerebral syphilis. Initial symptoms, left-sided headache and pains in legs. Polydipsia preceded polyuria. Marked excess of urine over fluids. Decided psychical disturbance. Severe vertigo and transitory attacks of left-sided hemiparesis and later a definite right-sided hemiplegia. Late history of hemianopsia attacks. Improvement in general condition under potassium iodide. Exaggerated knee-jerks.

W. A., male, single, 32 years of age, a stenographer, was admitted to Prof. Osler's wards in the Johns Hopkins Hospital for the first time on January 6, 1901, complaining of headache, thirst, passing of large quantities of urine, and of pain in the feet, left hip-joint and body.

His family history is unimportant. There is no history of diabetes, rheumatism, gout or tuberculosis. The patient has always been a healthy, active man until the onset of his present illness, with the exception of an attack of typhoid fever lasting 13 weeks when he was 19 years old. There is no history of gonorrhoea or lues, although there has been abundant opportunity for infection. There is a history of excessive sexual indulgence. He has always been a heavy cigar smoker, and he has used alcohol to excess. He began to drink at 18 and for several years he thinks he averaged a quart of whiskey a day. He usually took it undiluted, varied by an occasional mixed drink. He has drunk very little beer. He is active in his habits and his weight averages 160 pounds.

His present illness began in the summer of 1898 during the Spanish-American war. He was acting as stenographer in the War Department at Tampa, Florida. His work was exacting, and he was highly strung and excited over what he was doing. His first symptom was severe pain over the left side of the head. These headaches were constant, and he always woke up with them in the morning. Very soon he began to complain of pains in the legs. These were most severe in the knees and lower legs, and were aggravated by his going about. He kept at work as long as possible, but soon found that he could not keep things up to date. Six weeks after the onset of his illness he returned to his home in Washington, and remained in bed about one month. During this time he had the headaches and pains constantly. At about this

stage of his illness he began to notice that he was suffering from intense thirst and later that he was voiding abnormally large quantities of urine. He believes firmly that thirst was the first symptom. The amount was large and the urine was pale and had "no substance." In the latter part of 1898, he returned to his work in the War Department where he remained until about October, 1899. During this time he worked hard and was subject to pains every day in his head and legs. His polyuria and thirst continued. Since October, 1899, he has practically been unable to work. In October, 1900, he was passing about 2 gallons of urine in the 24 hours, and about two-thirds of this was voided during the night. He would often be up every half hour to urinate.

During the last month previous to admission he has been getting worse, and has been in bed most of the time. His strength and weight have failed. A short time ago swelling of the feet developed, the grade of which has varied. His appetite has never been ravenous, and recently it has been very poor. His bowels are very constipated. His sexual desire and power have been almost entirely lost since the onset of his present illness. He has slept poorly owing to the severe headaches and pains in the extremities.

The patient states that he thinks his mental condition has changed, and Dr. McCrae, who took the history of the case, states that it was quite evident that he had some mental disturbance. He would frequently change his statements, and declared on several occasions that he had two heads. He would break out in violent tirades against his previous physicians and employers. He was rather boastful of the amount of work he did, stating that it required two to do it after he gave up.

Physical Examination.—On January 7th I made the following note: The patient is well nourished but has apparently lost flesh, his present weight being 140¼ pounds. Skin is everywhere a trifle dry; considerable desquamation over the chest. There is no asymmetry of the skull or face. Complains of soreness on the left side of the head on percussion and on pulling the hair lightly. Percussion note on the left side of the cranium seems a little higher-pitched over the frontal and parietal regions. Left pupil is slightly smaller than the right; both react to light and accommodation. No strabismus; no hemianopsia. Tongue protruded in the median

line. There is no difference in the grip of the two hands nor in the strength of the two arms. The flexor muscles of the left thigh seem a trifle weaker than those of the right; otherwise the muscular power of the lower extremities seems equal. There is fairly marked dermatographia.

Romberg's symptom is present to a moderate degree. Body does not sway in any particular direction. *Reflexes.*—The triceps and radial are apparently normal. Both patellar reflexes are distinctly exaggerated. Epigastric reflex diminished; plantar increased; cremasterics normal. On light pinching of the skin there is decided hyperaesthesia over the entire left half of the abdomen.

The lungs are clear throughout on percussion and auscultation.

The point of maximum cardiac impulse is on the V interspace, just inside the mammillary line. Dulness is normal in extent. Heart sounds are clear at the apex and base. The liver flatness is normal; border of liver not palpable. The abdominal examination, excepting for the anaesthesia, is quite negative.

There is no evidence of any scar on the genitalia.

For several days after admission his headaches continued, but both his headache and his mental condition were much improved at the end of a week.

On January 16th, Dr. Randolph examined the patient's eyes and reported as follows: Slight hyperaemia of the left papilla. Disc outlines rather vague. Moderate degree of hypermetropia Right papilla apparently normal.

On admission the patient was started on 15-grain doses of potassium iodide three times daily, to be increased 5 grains every other day until he reached 100 grains three times a day. He received the iodide throughout his entire stay in the hospital. For periods of several days he received valerianate of zinc and ergotin as stated below.

Urine Examination.—The urine was greatly increased in amount. The smallest 24-hour amount was 5300 cc. and the largest 12,620 cc. It was almost colorless and ranged in sp. gr. between 1001 and 1004. It was either neutral or faintly acid in reaction. The examinations were persistently negative for albumin, sugar and casts. The urea determinations were always low; the amounts for four days were respectively 8.7, 9.7, 14.2, and 7.4 grammes.

The following table shows the extraordinary excess of urine over fluid taken:

CASE II. W. A. TABLE I.

Date.	Fluids taken.	Urine voided.	Fluids in excess of urine by	Urine in excess of fluids by	Remarks.
I, 9–10	7,680cc.	6,950cc.	730 cc.	....	Potassium iodide in increasing doses.
I, 10–11	6,225	5,300	925	....	
I, 11–12	6,995	6,400	595 ?	....	One voiding lost.
I, 12–13	5,360	5,140	220	....	
I, 13–14	7,295	8,000	....	705cc.	
I, 14–15	5,375	....	....	....	Urine lost.
I, 15–16	7,255	6,120	1,135	....	
I, 16–17	7,975	9,080	....	1,115	
I, 17–18	7,040	6,170	870	....	
I, 18–19	7,190	9,180	....	1,990	
I, 19–20	6,790	9,120	....	2,330	
I, 20–21	5,970	8,840	....	2,870	
I, 21–22	4,340	8,776	....	4,436	
I, 22–23	4,900	9,700	....	4,800	
I, 23–24	5,730	8,740	....	3,010	
I, 24–25	5,410	9,530	....	4,120	
I, 25–26	7,515	11,800	....	4,285	
I, 26–27	9,595	11,780	....	2,185	
I, 27–28	7,760	11,490	....	3,730	
I, 28–29	6,670	11,920	....	5,250	
I, 29–30	6,232	8,120	....	1,888	Zinc valerianate, gr. x, t. i. d., p. c.
I, 30–31	5,940	10,550	....	4,610	
I, 31– 1	6,572	8,960	....	2,388	
II, 1– 2	7,770	12,620	....	4,850	
II, 2– 3	6,330	10,020	....	3,690	Zinc valerianate, gr. xv, t. i. d., p. c.
II, 3– 4	5,560	11,915	....	6,355	
II, 4– 5	5,600	9,740	....	4,140	
II, 5– 6	6,170	10,510	....	4,340	
II, 6– 7	3,510	7,040	....	3,530	
II, 7– 8	5,720	9,700	....	3,980	
II, 8– 9	5,300	6,920	....	1,620	Zinc valerianate discontinued. Ergotin gr. ii, t. i. d., p. c.
II, 9–10	5,700	9,640	....	3,940	
II, 10–11	5,255	8,420	....	3,175	
II, 11–12	6,020	7,840	....	1,820	
II, 12–13	6,710	7,980	....	1,270	
II, 13–14	6,260	9,970	....	3,710	
II, 14–15	6,700	8,300	....	1,600	
II, 15–16	7,000	7,400	....	400	
II, 16–17	7,920	7,585	335	....	
II, 17–18	7,300	8,020	....	720	
II, 18–19	7,050	6,570	480	....	

An endeavor was made to ascertain the relationship between the fluids ingested and the urine eliminated in this case. The entire amount of fluids, including those taken with his meals, was carefully measured. The patient was in the general ward. There was no restriction placed upon the amount of water taken, so that there was no need of securing water surreptitiously. He was strictly enjoined not to take any fluids other than those measured out for him by the nurse.

February 13.—The blood count gave the following results: Red cells, 5,176,000; white cells, 12,800; haemoglobin 73 per cent.

February 18, 1902.—The patient is to be discharged from the hospital to-morrow. His general condition has markedly improved. The mental symptoms cleared up within two weeks after admission. Mind now perfectly clear. The headaches have entirely disappeared and the patient sleeps well at nights. His strength has steadily gained. He can now walk long distances without fatigue. There has been a steady gain in weight from 140¼ on admission to 159 to-day, an increase of 18¾ lbs. The polyuria persists without much change (see special urine chart). The thirst is still marked. The interesting feature of the case has been the marked increase in the amount of urine voided over the amount of fluids taken, notwithstanding there has been a steady increase in weight. On only a few days did the fluids exceed the amount of urine. On the other hand, the daily excess of urine over fluids ranged between 400 and 6355 cc.

From *January 19 to January 28* inclusive, when the patient was only on potassium iodide in increasing doses (which he also received later in addition to the zinc valerianate and ergotin), the average amount of urine was 10.169 cc.

From *January 29 to February 7* inclusive, patient was given valerianate of zinc (grs. x p.c. till February 2, and then gr. xv till February 8). Average amount of urine for the 10 days was 9.917 cc.

From *February 8 to February 17* inclusive, patient was given 2 grains of ergotin after meals. The average amount of urine was 8.107 cc.

COMPARATIVE TABLE.

	Average amt. of urine.	Treatment.
Jan. 19 to Jan. 28 inclusive....	10.169 cc.	K. I. in increasing doses.
Jan. 29 to Feb. 7 "	9.917	Valerian and K. I.
Feb. 8 to Feb. 17 "	8.107	Ergotin and K. I.

The patient's patellar reflexes are still very much exaggerated.

Eye Examination made this afternoon (Feb. 18), Dr. Randolph. Ophthalmoscopic examination negative.

On verbal communication with Dr. Randolph he stated that the injection of the left disc had entirely cleared up.

February 19.—Discharged. To continue potassium iodide.

Second Admission.—The patient was re-admitted on June 17, 1901. After leaving the hospital he remained comparatively well for some time. Several weeks ago he began to notice that his gait was slightly uncertain in the dark, and he occasionally complained of dizziness. On two or three occasions he has complained of a numbness and heaviness in the left arm and leg. On the morning of admission, while coming down stairs, he suddenly experienced a sensation of heaviness in the left leg and arm. Both extremities felt as though they were asleep. He was forced to sit down on the steps. For two minutes he was unable to move either the arm or leg. Five minutes later the strength had entirely returned and he felt perfectly well again. On physical examination there was nothing made out not already noted on the previous admission. There was no evidence of any unilateral muscular weakness. The knee-jerks were still exaggerated. The patient's mental condition was undoubtedly changed. He was very boastful and gave exaggerated accounts of things he had been doing. He only remained in the hospital until June 22. The amount of urine had materially diminished since the previous admission. It ranged between 4960 and 6220 cc. The fluids on this admission exceeded the amount of urine by between 1295 and 2405 cc. The patient had been taking about 90 grains of potassium iodide three times daily.

Third Admission.—The patient was admitted to the hospital a third time on December 1, 1901. He stated that on August 5 he had a serious attack of vertigo while walking on the street. He fell and struck his head against the curb-stone and was rendered unconscious for more than 24 hours. His mental disturbance continued. Unintentionally he bought a ticket in Washington, and did not realize what he had done until he found himself in New York.

On November 21, 1901, the patient decided to take up active work again and secured a position as confidential clerk to an editor of one of the Washington papers. On November 28, he found on

getting out of bed at 10 a. m. that he had practically no use of his right leg. He soon returned to bed, and later in the day he lost the power in his right arm. Articulation became difficult, and he could not speak louder than a whisper. When the patient entered the hospital four days later, there was still almost entire loss of power on the right side, including the lower facial muscles on the same side. There was some return of the power of the muscles of the right lower extremity. He still had difficulty in articulating. The eye-grounds were normal.

Urine Examination.—The amount of urine on this admission ranged between 5100 and 9180 cc. The patient was unable to get out of bed, the fluids and urine more nearly equal than on either of the previous admissions. On some days the amount of the fluids and on others that of the urine was in excess. The nitrogen, chlorides and phosphoric acid were determined for five days. The patient was on a comparatively light diet during the examination. The following table gives the results for these five days:

CASE II. W. A. TABLE II.

Date.	Fluids.	Urine.	Sp. Gr.	Nitrogen.	Chlorides.	Phosphoric Acid.
XII 7–8.....	8640	8500	1001	14.2800	6.800	3.6890
XII 8–9.....	6970	7240	1001	11.8736	7.964	3.0408
XII 9–10.....	8830	8490	1002	11.8860	7.641	2.8866
XII 10–11.....	9130	8860	1002	12.0496	6.207	3.7212
XII 11–12.....	9180	10930	1002	14.0997	16.395	2.0439

When the patient was discharged from the hospital on December 21, he was ordered to continue the potassium iodide and the mercurial inunctions which had been administered while in the hospital.

February 12, 1902.—A letter received from the patient to-day states that the power is gradually returning in the right arm but that he is still unable to write. Until one week ago the thirst and urine were decidedly diminished. During one night from 10.30 p. m. until 7.30 a. m. he only drank 300 cc. of water. For the last few days, however, the thirst has returned and he drinks from

five to six quarts daily. He states that the intake of fluids is decidedly in excess of the urine voided. Has no headache at present.

March 17, 1902.—The patient returns for observation to-day. His general condition is good. The paralysis has entirely cleared up. Polyuria and thirst persist, but are less marked. He gives a history of what are apparently hemianopsia attacks. He relates that at times he is able to see only the half of printed signs. There is no hemianopsia at present.

Case III. (Hospital No. 35321.)

Diabetes Insipidus of doubtful origin. Laborer in a copper foundry. Typhoid fever seven months before onset. Unconsciousness and left-sided convulsive movements of the arm and leg preceded the thirst and polyuria by about three weeks. Polydipsia preceded polyuria. Amount of fluids exceeded that of urine. Night urine greater than that during the day. Knee-jerks diminished.

J. W., male, single, aged twenty-five, German, laborer in a copper foundry, was admitted to the Johns Hopkins Hospital, under Prof. Osler, on June 28, 1901, complaining of intense thirst and the passing of enormous quantities of urine.

There was nothing of importance in the family history. There was no history of diabetes insipidus. The patient had always been well previous to coming to this country nine years ago. For three years after his arrival, he had worked in a copper foundry at Canton, Md., where he says the atmosphere was foul and dusty. Subsequent to this he worked on a farm for five years. In 1896 he had malarial chills every other day. These were stopped in six days by medical treatment. In August, 1899, the patient was treated in the Johns Hopkins Hospital for double tertian malarial fever. This was a mild infection, the patient remaining in the ward for only eight days. On September 24, 1900, he was again admitted to the Johns Hopkins Hospital suffering from typhoid fever. The attack was a comparatively mild one and ran the usual course without any special complications. He was discharged on October 24, a month later. There was no polyuria at this time, the amount of urine ranging from 500 to 1300 cc. in the twenty-four hours. Since his recovery from typhoid fever,

he has worked off and on in the copper foundry at Canton. In April, 1901, he suddenly became unconscious, and says that during the unconscious spell, he had convulsive movements in the left arm and leg. His left eye also was affected in some way, and was treated for it at the Presbyterian Eye and Ear Infirmary, Baltimore. He also suffered from ringing in the left ear. The patient states that previous to the onset of the attack of unconsciousness he had suffered from severe headaches. At the onset of the sudden illness he was taken to the Canton station house, and thence to the Towson jail, where he was kept one week. After this he was confined in the Alms-house for five weeks, leaving this institution very much improved, and remaining with friends in the country for two weeks.

The patient has been a very heavy drinker, taking from fifteen to twenty glasses of beer daily. For the past ten weeks he has taken very little alcohol, thinking possibly his illness was caused by drinking; has not had an especially large appetite; uses tobacco moderately; denies all venereal infection; bowels usually regular.

The present illness began four weeks ago while he was an inmate of the Alms-house. He first noticed intense thirst, and shortly afterwards that he was voiding large quantities of urine. On one occasion he measured his urine for twenty-four hours and found the amount to be $3\frac{3}{4}$ gallons (15,000 cc.). He voids urine every hour. The thirst is excessive, and he thinks he drinks from five to six gallons per day. He states the amount of urine has gradually increased up to the present. He has not had any headache nor any pain in any part of the body since onset of polyuria. Has no vertigo. Thinks his eyesight in the left eye is impaired, and complains of occasionally seeing double at night. He has had no mental symptoms since the onset of the present illness; has not complained of being especially weak; not short of breath on exertion; has not had any fever.

Physical Examination.—The patient is of medium stature, and on admission weighs $140\frac{1}{4}$ pounds. He is well nourished; face and mucous membranes good color. The tongue is a trifle coated and protrudes in the median line. There is no facial asymmetry; movements of facial muscles good. There is no asymmetry of the skull. The pupils are normal in size and equal; react to light and accommodation. There is no strabismus nor hemianopsia. There is no

stiffness of the knee muscles. The temperature on admission yesterday reached 101° at 8 p. m. This morning at eight a. m. it is 95.8°. The pulse is of good volume and tension; regular in force and rhythm; 68 to the minute; vessel wall just palpable.

The lungs are perfectly clear throughout on percussion and auscultation. The point of maximum cardiac impulse is in the fourth interspace 9 cm. from the median line. The heart sounds are clear at the apex and base. The liver dulness is normal in extent; border of liver not felt.

The spleen is firm and is distinctly felt just at the costal margin at the end of deep inspiration. The abdominal examination is practically negative. Neither kidney is palpable.

There is no general glandular enlargement, but the inguinal and epitrochlear glands are slightly enlarged.

There is no evidence of a scar on the genitalia; the epididymis is normal on both sides. The knee-jerks are diminished, being just obtainable on re-enforcement. There is a distinct Romberg symptom. The patient shows marked ataxia in walking, and follows a line with difficulty. There is slight inco-ordination of the movements of both upper extremities.

June 30, 1901.—The blood examination gave the following results: Red blood corpuscles 4,312,000; leucocytes 11,300; haemoglobin 65 per cent.

July 2, 1901.—The examination of the eyes was made by Dr. H. O. Reik, who reports as follows: There are some curious changes about the blood vessels that one cannot explain, and some minute deposits in the retina or choroid suggestive of what one sees in diabetes mellitus, but nothing that we can say is pathognomonic.

Urine Examination.—The urine during the entire stay of the patient in the hospital was enormously increased, the amounts ranging from 7330 cc. to 13,330 cc. for the twenty-four hours. The daily average being 10,002 cc. It was extremely pale, faintly acid in reaction, the sp. gr. ranging between 1000 and 1003, on several occasions the former sp. gr. being observed. At no time were any sugar, albumin or casts found in the urine.

For the purpose of ascertaining the relationship between the fluids ingested and the urine voided, both were carefully measured for a period of twenty days (June 29 to July 19). During this

time the patient was not isolated, but was in the general ward. On twelve of the days the fluids ingested exceeded the urine voided; the highest excess being 6870 cc. during one day. On the other eight days the urine voided exceeded the fluids ingested, the highest excess being 3210 cc. The daily averages of the fluids ingested and of the urine voided for the twenty-four hours was 10,543 cc. and 10,002 cc. respectively for the twenty days, showing that the daily average of fluids ingested exceeded that of the urine voided by 541 cc.

With the exception of the first day of admission, when the patient's temperature reached 101°, he had practically no fever during his stay in the hospital. The patient was allowed a generally light diet, and the medicinal treatment consisted in the administration of potassium iodide in increasing doses, so that when discharged from the hospital on July 19, he was receiving thirty grains three times a day. When he left the hospital there was no material improvement in his condition, the amount of urine for the last twenty-four hours being 11,520 cc.

For the last few days that the patient was in the hospital the records of the urine and fluids for the day and night were calculated separately. They showed that for the 12 hours from 7 p. m. to 7 a. m. the patient voided more urine but ingested less fluid than for the twelve hours from 7 a. m. to 7 p. m.

Case IV.

Diabetes Insipidus probably of syphilitic origin. Passage of two renal calculi two years before onset. Symptoms preceded by headache for three or four months. Disease supposed to have followed an attack of influenza. Marked loss of weight and extreme asthenia. Distinct vertigo and ataxia. Double abductor paralysis of the vocal cords. Paralysis of right palatal muscles. Early diminution of thirst and urine under potassium iodide and later an extraordinary gain in weight and strength under the same treatment.

E. F. B., male, aged 36, single, mechanical engineer, consulted me on July 14, 1900, complaining of general weakness and loss of voice.

The family history was unimportant with the exception that

his gradfather had a "cancer on the hand" and one maternal aunt had tuberculosis. There was no history of diabetes insipidus in the family.

The patient had pneumonia at 16. Eight years ago he complained of rheumatic pains in the hips and shoulders. He had never been subject to cough. Ten years ago he smoked a great deal; smokes much less at present; drinks in moderation; had gonorrhoea at 22; denies luetic infection. Two years ago he suffered from renal colic on the right side; passed two calculi the size of buckwheat grains. For two or three years the patient had been residing at Painesdale, Houghton Co., Michigan, where he had been engaged as a mining engineer.

The present illness began in January, 1900. I am indebted to Dr. Charles Drummond, of Painesdale, Houghton Co., Michigan, for the following notes of the early history of the patient's illness:

"In the fall of 1899, I made E. F. B.'s acquaintance. He was Master Mechanic at this mine. One evening I noticed him acting as if he did not feel well. Inquiry elicited the answer that he had been suffering from violent headaches. Further questioning made me believe that he was suffering from the after effects of a residence in a malarial country. I acted accordingly, and was pleased after about 6 weeks' treatment to find that he was immensely better. He remained first rate till in the early winter, when he took the grippe. This laid him up for nearly two weeks. He never seemed entirely well after that, and within a month or so, he apparently began to "go down hill." Repeated examinations failed to elicit any tuberculous symptoms, although I found a suppurating cervical gland. He was kept on a straight tonic treatment for some time, and when that seemed so disappointing, he was also put on Potassium Iodide and Ext. Cinch Co. I examined his urine repeatedly, and obtained no albumin, no sugar, the specific gravity being 1003 to 1005. The quantity passed per diem I never estimated, but it soon became enormous. He himself stated that it must be a couple of gallons, if not more. His thirst was simply astounding to all who knew him. He was forever emptying all the engineer's pails in the boiler houses, and wherever one would meet him, he was always munching at an icicle. As spring came on it was apparent to us all, that he was

failing fast, but such was his devotion to his work, that he would heed no warnings.

"His work in the early stage of the development work of the mine was very exacting, demanding a great deal of walking, over very rough ground. In addition to this, he was very conscientious and worried very much over the work. He would never tell me how weak he really was, but from the mining captain one day I learned that he found him completely exhausted in the bush, and it was only with his help that the patient was able to get back to camp.

"Again and again, I had urged him to throw up the work, believing that the very worry through which he was passing, was going to master him completely. All my efforts were of no avail, till he was actually too weak to do the work, when he was reluctantly forced to acknowledge that he must quit."

From the patient himself it was learned that he had high fever during his attack of grippe, which occurred in January, 1900, and that he was confined to bed for several days. He stated, on one occasion, he measured his urine for twenty-four hours and found that the quantity was four gallons, or approximately 16,000 cc. His thirst lasted until about May 1, 1900, when he thinks it was stopped by the medicines administered. The polyuria also practically disappeared at this time. Neither the thirst nor the polyuria have returned to any marked degree since then. His appetite has always been poor. He lost weight rapidly at the beginning of the illness, losing 30 pounds in two weeks. He does not think he has emaciated since. He has suffered from headaches at intervals ever since the onset. There has never been any oedema of the feet. He does not have to urinate during the night now. There has never been any cough. Dyspnoea has been a marked symptom since the grippe attack. He has become decidedly weak, and is easily fagged out. Seven weeks ago his voice began to grow husky. The hoarseness has persisted up to the present date. There is no soreness of the throat on swallowing. In drinking, there is a tendency for the fluids to return through the nostrils. For two weeks he has been suffering from nausea and vomiting. He vomits just after rising in the morning.

Physical Examination.—Patient is of fairly good color; conjunctivae slightly injected; tongue clean; pulse 120 to the min-

ute; temperature 99.4°; weight 130 pounds. His voice is distinctly husky, and the patient is markedly dyspnoeic. He is manifestly weak and the slightest exertion causes shortness of breath and fatigue. Later, when observed leaving the hospital it was noticed that his gait was quite unsteady. There is a scar on the right side of the neck resulting from a suppurating gland which was opened three years ago. The pupils are equal and react to light and accommodation. The thorax is well formed. The lungs are clear on percussion and auscultation. The heart sounds are everywhere clear. The abdomen looks natural. The liver flatness just reaches to the costal margin in the mammillary line; the border is not palpable. The spleen also is not to be felt. There is no oedema of the feet. On examination of the pharynx the palatal muscles and pillars of fauces are paralysed on the right side. Laryngoscopical examination made by Dr. Warfield shows bilateral abductor paralysis of the vocal cords. There is no evidence of a scar on the penis. The patient was put on strychnine sulphate gr. 1/30 three times a day after meals.

Sputum Examination.—A small quantity of fluid sputum was obtained; not muco-purulent; no tubercle bacilli found.

Urine Examination.—A fresh specimen was of a very pale color; neutral; specific gravity, 1002; absolutely clear; no sediment. It contained no albumin or sugar. The centrifugalized specimen showed no casts, but a few epithelial cells.

July 19, 1900.—Patient returns practically unimproved; has nausea and vomiting before breakfast each morning. On July 17 he weighed 130 pounds. His pulse is 112 to min.; temperature 99.2°. Two specimens of urine were brought; they were both extremely pale and faintly acid in reaction; the evening specimen had a sp. gr. of 1006, the morning specimen 1003; there was no sugar, no albumin nor casts in either specimen.

July 25, 1900.—The patient measured his urine for the last twenty-four hours and found the quantity to be five pints and one gill or approximately 2600 cc. This indicates that the patient is still voiding more urine than normal. It is pale, acid, sp. gr. 1005 and contains no albumin nor casts. During this 24 hours the patient drank six pints of fluids or approximately 3000 cc. He thinks he is a trifle stronger; weight is 131½ pounds; gait is unsteady. Romberg's symptom slightly marked; there is a ten-

dency for the body to sway towards the left. Pupils are equal; react sluggishly to light. There is no hemianopsia. Still has occasional frontal headaches on the left side. There is also pain in the left eye. He complains of vertigo. The examination of the lungs shows suggestive impairment of the percussion note in the right interscapular region. Otherwise the lungs are practically negative. An important feature is the marked exaggeration of both knee-jerks. The eye-grounds have been examined by Dr. J. J. Mills, who reports that the examination is negative. There is, however, some astigmatism.

August 1, 1900.—Patient's condition is practically the same. The nausea and vomiting continue. The voice seems slightly less husky. The patient was given bismuth subnitrate and codeia sulphate for the nausea.

August 15, 1900.—Practically unimproved; there has been no gain in weight; nausea persists. The twenty-four hours amount of urine from August 12 to 13 was four pints (2000 cc.). During this same time he drank six pints (3000 cc.) of fluids. Knee-jerks are still exaggerated. The patient not having improved under rest, dieting and strychnine, it was decided to commence the administration of potassium iodide, 15 grains three times a day after meals being administered.

October 8, 1900.—The patient has not been seen since last date. His condition, however, began to improve immediately after the commencement of potassium iodide, and the improvement has continued up to the present. His appetite is better. He has absolutely no nausea, and his present weight is 157 pounds, being a gain of 25½ pounds in a little over six weeks. His gait is steadier, and there is now no tendency for the body to fall to the left. The headaches have entirely disappeared. The Romberg symptom is now absent. The knee-jerks are still much exaggerated. The patient is to continue taking potassium iodide, increasing the dose until 30 grains are taken three times a day.

February 12, 1902.—I received a communication from the patient's father to-day stating that in January, 1901, his son accepted an appointment with a Philadelphia firm and went to London, England, to look after their interests there. A letter had been received from him in November, 1901, stating that his health was much improved and his voice very much stronger.

Case V.

Diabetes Insipidus due to cerebral syphilis. Dragging of the right leg and severe cerebral symptoms with unconsciousness of a week's duration preceded the onset of thirst and polyuria. Recurring transitory attacks of hemianopsia, an early symptom of the cerebral disease. Urine in excess of fluids. Day urine exceeded night urine. Knee-jerks exaggerated.

L. R., aged 35, from Ohio, seen with Prof. Osler, February 7, 1902, complaining of great thirst.

Family history excellent.

Personal History.—Always very strong and well as a young man. Thirteen years ago he had syphilis, but was very well and thoroughly treated. He had lived freely and smoked very heavily. Married nine years ago; has healthy children. Three years ago he had an attack of what the doctors said was cerebral syphilis. For several weeks he had had a little dragging of his right leg. In 1898, while on a cruise in Cuban waters, he noticed that for periods of five minutes at a time he would lose his sight over one-half of his visual field. He does not recollect what portions of the field of vision were affected. These attacks of hemianopsia would clear up and recur many times in the twenty-four hours. This interesting symptom lasted for a month and has not returned since. Then one evening, while watching a game of billiards, he felt very badly, had severe headache, went to bed, and the next morning had a very severe attack in which he was blue for hours; was critically ill; the breathing was very light and quiet, and for some time they did not think he would recover. He remained unconscious for a week, and his temperature was very much subnormal. After he recovered consciousness he talked at random, and did not know where he was for a time. No paralysis followed. He states that for some time before this attack he had had severe headaches at intervals. The severe attack was in October, 1899. He gradually recovered, but during the convalescence he noticed that he had the most unquenchable thirst, which has persisted without interruption ever since, and for it he seeks relief. During the past three years he has remained in good condition. His physical health is perfect. He has had no headaches, has been able to go hunting, but, as he expresses it, he simply lives to drink. He says that he

passes no moment without thinking about it. He will drink literally quarts of cold liquids at a time. He has passed from eighteen to twenty pints of urine in the twenty-four hours. He does not perspire over the body, but most profusely about the forehead and face in hot weather. No treatment seems to have been of any avail. He has taken potassium iodide up to 150 drops of the saturated solution in the day. He drinks chiefly cold things. During the day he can go for an hour and a half without drinking. At night he wakes five or six times to drink and to pass water. Next to his thirst the most distressing symptom at the present time is the existence of severe racking pains in the lumbar region. These are worse at night and interfere with his sleep.

Examination.—Remarkably healthy looking man, of good color and fine physique, weighs 204 pounds. The arteries are not sclerotic. The pulse is slow, regular and no increase in tension. The tongue is red and clean. Pupils of medium size, equal, react to light and accommodation; ocular movements perfect. Movements of the facial muscles are normal; no trace of any residual paralysis. The hearing is good. Taste and smell normal. The examination of the abdomen is normal. The liver is not enlarged; the right lobe can be felt on deep inspiration, not hard. The spleen is not palpable. The apex beat of the heart not visible, not palpable; no increase in the area of cardiac flatness. Heart sounds are clear at apex and base. The station is good; stands well on either leg. The knee-jerks are slightly exaggerated. Tactile, thermic and painful sensations everywhere perfect.

Urine Examination.—The urine is almost colorless, neutral, sp. gr. 1002. There is no reaction for albumin or sugar. There are no casts.

At Dr. Osler's suggestion, this patient entered the Johns Hopkins Hospital on March 10, 1902, in order that his case might be more carefully studied.

He was placed on the following diet for the five days during which the analyses were made:

REGULATED DIET FOR PERIOD OF ANALYSIS.

Breakfast.—300 cc. coffee; 120 cc. cream; 150 grams lean beefsteak; 10 grams white bread; 20 grams butter; water ad libitum.

Dinner.—100 grams warm or cold roast beef (lean); 60 grams boiled white potatoes; 5 grams white bread; 5 grams butter; 3 tablespoonfuls boiled rice; 150 cc. milk; 2 tablespoonfuls of spinach, green beans or peas; water ad lib.

Supper.—50 grams lean cold ham; 2 boiled, poached or scrambled eggs; 10 grams white bread; 10 grams butter; 300 cc. tea, with sugar and lemon; water ad lib.

Late Supper.—2 soft-boiled eggs; 10 grams bread.

N. B.—3 grams of salt to be used during the 4 meals. 30 grams of sugar to be allowed each day. Patient to have all the water he requires to quench his thirst.

For a period of five days the nitrogen, urea, chlorides and phosphoric acid were determined with the patient on the above diet. The nitrogen was estimated by the Kjeldahl method; urea by the hypobromite process; chloride by Arnold's method, and the phosphoric acid by the uranium nitrate method. Table I gives the results of the analyses.

TABLE I.

Date.	Weight.	Fluids.	Urine.	Total Nitrogen.	Urea.	Phosphoric Acid.	Chlorides	Remarks
	lbs.							
III, 14–15	194¼	6250	6620	14.6964	26.48	2.1250	7.9440	——
III, 15–16	194½	5970	6800	15.3000	23.80	2.2440	8.5000	——
III, 16–17	194¼	6350	7450	14.1550	26.07	2.1158	8.9400	——
III, 17–18	196	6990	7830	15.5817	28.97	2.0671	10.9620	——
III, 18–19	195	6610	7070	15.5540	26.15	2.2199	12.7260	——

It will be seen from a study of the above table that the various constituents of the urine estimated were all within normal limits. The intention had been to determine the balance between the nitrogen intake and output, but owing to an accident to the collected feces during the process of evaporation this was unfortunately not possible.

In order to determine the relationship between the intake of fluids and elimination of urine all the fluids (including those taken with the meals) were carefully measured during the five days. An interesting point was brought out, namely, that the urine for each

day exceeded the intake of fluids by from 370 to 1100 cc. This is shown in Table II.

TABLE II.

Date.	Fluids.	Urine.	Excess of Urine over Fluids.	Remarks.
III, 14–15	6250	6620	370	——
III, 15–16	5970	6800	830	——
III, 16–17	6350	7450	1100	——
III, 17–18	6990	7830	840	——
III, 18–19	6610	7070	460	——
, 19–20	6810	8300	1490	Additional day.

The relationship of the intake of fluids and elimination of urine for the day and night is shown in Table III. Contrary to what is usually stated to occur in diabetes insipidus, the night urine was less than the day urine. This corresponded with the difference in the quantity of fluids drank, the amount of the fluids during the day being in excess.

TABLE III.

Date.	Fluids.			Urine.			Remarks
	7 A. M.–7 P. M.	7 P. M.–7 A. M.	Total	7 A. M.–7 P. M.	7 P. M.–7 A. M.	Total	
III, 14–15	4040	2210	6250	4200	2420	6620	
III, 15–16	3720	2250	5970	3100	3700	6800	
III, 16–17	4300	2050	6350	4100	3350	7450	
III, 17–18	4550	2440	6990	5230	2600	7830	
III, 18–19	4270	2340	6610	4230	2840	7070	
III, 19–20	3970	2840	6810	3910	4290	8300	

On March 20th, Dr. Osler examined the patients' eye-grounds and made the following note: Both discs are clear. The margins are well defined. Arteries not sclerotic. No retinal changes.

SUMMARY.

1. The old classifications of cases of diabetes insipidus under the headings of hydruria, azoturia and anazoturia is no longer tenable, the nitrogenous constituents of the urine being almost entirely dependent on the nature of the food.

2. Animal experiments have taught us much regarding the lesions of the central nervous system which are capable of producing either a temporary or permanent polyuria.

3. Clinically the cases of diabetes insipidus come under two headings:

a. The primary or idiopathic cases—those in which there is no evident organic basis for the disease.

b. The secondary or symptomatic cases—those attributable to definite organic changes either of the nervous system or abdominal viscera; to physical disturbances, etc.

4. It is difficult to decide in which group certain border-line cases should be placed.

5. Some observers classify those cases, in which thirst is the first symptom, as an independent disease under the name of primary polydipsia. The evidence in favor of this view at the present time does not seem to be sufficient.

6. Tumors involving the medulla and floor of the fourth ventricle, cerebral haemorrhages, and basilar meningitis are the commonest organic lesions causing the disease.

7. Cerebral syphilis is apparently the cause in a larger number of cases than is generally supposed, the lesion most frequently being a syphilitic basilar meningitis.

8. Diabetes insipidus is uncommon in this country, only 4 cases or 0.001 per cent, occurring out of a total of 356,637 cases treated at the Johns Hopkins Hospital and Dispensary.

9. The 5 cases here reported were all in males, their respective ages being 44, 32, 25, 36, and 35 years.

10. The longest duration of the disease was 10 years (Case I).

11. Four of the five cases gave evidence of marked cerebral disturbance.

12. One case (Case I) belongs to the primary or idiopathic group; the other four being regarded as secondary or symptomatic cases.

13. Case V was undoubtedly due to cerebral syphilis. Cases II and IV were in all probability due to the same disease. Case III was apparently due to cerebral disease, as evidenced by the history of convulsions and unconsciousness preceding the onset. Case I was of unknown origin.

14. In all 5 cases thirst appears to have been the first symptom; at least it seems to have been the first that attracted attention.

15. An interesting finding was the presence of exaggerated knee-jerks in 4 of the cases. In the other case (Case III) they were diminished.

16. There is usually no marked disturbance of the metabolic functions. Worthy of note, however, is the fact that in Case I the patient added over 49 grams of nitrogen to his body with a very slight loss of weight.

17. The nature of the disease is still uncertain. What can be said with certainty is, that it is due to some nervous influence causing a vaso-motor disturbance of the renal vessels, leading to constant congestion of the kidneys.

18. There is no constant anatomical finding at autopsy. The most frequent one is enlargement and congestion of the kidneys.

19. The prognosis is much less favorable in the secondary or symptomatic cases.

20. The treatment is very unsatisfactory. Therapy usually fails to give relief. In the syphilitic cases antiluetic treatment at times causes a marked improvement in the general health as in Cases II and IV, and also occasionally an almost complete cessation of the thirst and polyuria as in Case IV. On the other hand syphilitic treatment may be of no avail, as in Case V.

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OBSERVATIONS ON THE ORIGIN AND OCCURRENCE OF CELLS WITH EOSINOPHILE GRANULATIONS IN NORMAL AND PATHOLOGICAL TISSUES.

By W. T. HOWARD, JR., M. D., AND R. G. PERKINS, M. D.

(From the Pathological Laboratory of Lakeside Hospital, Cleveland, Ohio.)

(Plate VIII.)

In the routine examination of 825 specimens derived from operations, and of the organs from 120 autopsies from the various services of Lakeside Hospital, we have been struck with the frequency with which cells with eosinophilic granulations have been found. It is our purpose in this article to classify and analyse these observations.

By the terms "eosinophile and eosinophilic cell," and "cell with eosinophilic granulations" as used in this article, we mean a cell with coarse or moderately coarse granulations which stain deeply and intensely with acid dyes, especially with eosin. These cells correspond to the eosinophilic cells of human blood of Ehrlich, and to the coarsely granular oxyphile cell of Kanthack and Hardy. All cells with homogeneous non-granular protoplasm, as well as the polymorphonuclear neutrophilic cell of Ehrlich or the finely granular oxyphilic cell of Kanthack and Hardy, are excluded from consideration.

Methods.—Most of the tissues upon which this study is based were hardened in Zenker's fluid, some in Orth's fluid, and a few in 95 per cent alcohol. The best results were obtained with Zenker's fluid. Celloidin was commonly used for embedding, though the paraffin method was used in some cases. As a matter of routine sections were stained in haematoxylin followed by a rather strong aqueous solution of eosin which was allowed to act for a short time Overstaining with eosin was studiously avoided. In most cases there was no intention of staining for eosinophilic granulations, but the sections were stained in the usual manner by a number of different workers from the various services of the

hospital. Sections from a number of cases were stained with eosin followed by methylene-blue, which gave good results. Besides eosin in special cases other acid dyes, such as acid fuchsin and picric acid combined (Van Gieson's stain) the Biondi-Heidenhain and the Ehrlich triacid stains, were tried and always with positive results.

Sections which showed large numbers of eosinophiles were treated with freshly-prepared ammonium sulphide for from six to twenty-four hours but in no case were any of the granules changed in color. Sections treated with fresh potassium ferrocyanide also failed to show the presence of iron.

For convenience we shall classify our observations as follows:

Observations on the presence of cells with eosinophilic granulations in (I) apparently normal organs (II), in pathological tissues in material derived from operations, (III) in organs showing pathological changes in cases coming to autopsy.

I. Cells with Eosinophilic Granulations in Apparently Normal Organs.

In ten normal appendices these cells were numerous; in five cases they were confined to the stroma of the mucosa, in two they were in both the stroma and in the lymphoid tissue, while in three they were numerous in the stroma with a few in the capillaries. A few eosinophiles were found in the blood-vessels of a normal Fallopian tube.[1]

They were found in apparently normal organs in the following cases coming to autopsy:

Case I. A few polymorphonuclear eosinophiles were present in the kidney of a five days old infant with omphalitis and *Staphylococcus aureus* bacteriaemia.

Case II. A child one month old, dead of streptococcus infection. A few polymorphonucler eosinophiles were present in the mucosa of the ileum.

[1] Since the above was written we have examined a large number of both normal and inflamed appendices, in nearly every one of which there were large numbers of eosinophiles. In the normal appendix they are confined to the interglandular stroma and the lymphoid tissue, while in inflammation they invade all coats. They are much more readily found after hardening in Orth's or Zenker's fluids than in alcohol.

Case III. In a still-born child, seven months in utero, the liver capillaries contained large numbers of polymorphonuclear eosinophiles.

Case IV. In a child with imperforate anus, dead three days after birth, the muscularis of the rectum at the point of atresia showed numerous round cells, and a few polymorphonuclear eosinophiles.

Case V. In a case of epidemic cerebro-spinal meningitis, due to *Diplococcus intracellularis meningitidis*, a few polymorphonuclear eosinophilic cells were seen in the stroma of the mucosa of the small intestine.

Case VI. In a case of a child two days old, in whom death followed gastro-intestinal haemorrhage, due probably to haemophilia, polymorphonuclear cells with eosinophilic granulations were found in numbers in the connective tissue of the portal spaces in the liver.

Case VII. In a child two weeks old, dead of follicular dysentery and omphalitis, the latter due to *Staphylococcus pyogenes aureus*, there was marked congestion of all the organs, including the thymus. The lymphoid tissue of the latter organ contained large numbers of coarsely granular eosinophiles. A few of these cells had small deeply staining reniform or polymorphous nuclei. Most of them, however, had a single round, oval, or reniform slightly vesicular nucleus resembling in all respects the nucleus of the plasma cell. The nuclei of many of these cells were eccentric. In some plasma cells nuclear figures were seen.

There was no special relation of the eosinophiles to Hassal's bodies. The eosinophiles were most numerous at the peripheral portions of the glands.

In four of the seven cases there was infection, septicaemia occurring in two. In these four cases the infectious agent may have stimulated the formation of the eosinophiles.

II. Cells with Eosinophilic Granulations in Pathological Tissues in Material derived from Operation.

In twelve cases of acute appendicitis, these cells were numerous in the tissues of five, in the tissues and vessels of one, and very numerous in the tissues and vessels of two, and very numerous in the tissues in four.

In six cases of chronic appendicitis, a few were found in the tissues and exudate in two, and in the other four they were numerous in the tissues.

In six cases of salpingitis, one of which was tubercular, a few were found in the stroma of the mucosa and in the muscularis. In four cases a few occurred in both vessels and tissues, in six cases there were a few in the blood-vessels, and numbers in the tissues; in eight cases they were numerous in the tissues and absent from the blood-vessels; in eight cases they were numerous in both vessels and tissues; in one case they were numerous in the vessels and very numerous in the tissues; in two cases they were very numerous in the tissues and absent from the blood-vessels; in one case they were very numerous in both vessels and tissues, and in one case they were present in small numbers in the vessels and in great numbers in the tissues, making thirty-seven cases of salpingitis in all.

In one case of acute ovarian abscess they were present in small numbers in the tissues, while of eight cases of chronic ovarian abscess they were present in the tissues in small numbers in one case, in large numbers in two cases, and in great numbers in four cases, but were absent from the blood-vessels, while in two cases they were present in great numbers in both tissues and blood-vessels.

In two cases of acute perioophoritis they were present in both vessels and tissues in large numbers. In four cases of chronic perioophoritis they were present in the tissues in small numbers in one case, in large numbers in another case, in very large numbers in a third case, while in the last case they occurred in small numbers in the blood-vessels and in large numbers in the tissues.

In two corpus luteum cysts they were numerous in the tissues in one case, present in small numbers in the vessels and very numerous in the tissues of the other.

In one case of congestion of the Fallopian tube they were present in numbers in the blood-vessels.

In a case of inflammatory thickening of the broad ligament they occurred in numbers in both blood-vessels and tissues.

In one case of hypertrophic endometritis a few were found in the tissues, and in a case of acute interstitial endometritis after abortion, a few were present in the blood-vessels and large numbers in the tissues.

In three cases of carcinoma uteri they occurred in one case in numbers in both vessels and tissues, in the other two cases in great numbers in the tissues while none were found in the blood-vessels.

In two cases of epithelioma of the vagina numbers were found in the tissues in one case, a few in the vessels and great numbers in the tissues in the other case.

In one *Staphylococcus aureus* abscess of the gland of Bartholin numbers were found in the tissues but none in the blood-vessels.

Two cases of proctitis showed very large numbers in the tissues.

One case of pilonidal abscess showed numbers in the tissues, but none in the vessels.

In three cases of omentitis one showed numbers in the tissues, but none in the vessels, the second, numbers in both blood-vessels and the tissues and in the third none in either the vessels or the tissues. In one case each of carcinoma of the arm, secondary epithelioma of a lypmh gland, epithelioma of the scrotum, and in two cases of epithelioma of the face they were found in the tissues in numbers. They were present in the tissues in varying numbers in cases of tuberculosis involving the following organs: striated muscle, anus, rectum, ureter, cervical lymph glands, and skin. In three nasal polyps numbers of eosinophiles were present in the tissues in two and in the tissues and blood-vessels in one. They were numerous in the lesions in six cases of osteomyelitis, three of which were tuberculous. They were found in considerable numbers in the tissues in one case of gonorrhoeal lymphangitis and in a gumma of the skin.

For comparison with the foregoing some fifty cases of inflammatory and other lesions of various tissues were noted in which eosinophiles were absent. Among these there were twenty cases of acute and chronic salpingitis, three cases of abortion remnants, three of endometritis, and several corpus luteum cysts.

Altogether coarsely granular eosinophiles were present in either the tissues, exudates or blood-vessels in 108 out of 825 consecutive specimens derived from operation, or in 13.09 per cent of the cases; 80 of these cases were inflammatory, 24 being acute and 56 chronic. Appendicitis was the lesion in one-half of the acute cases. There were 9 cases of tuberculosis and 9 of syphilis; 9 of the 16 non-infectious cases were carcinomata and 3 were nasal

polyps. We have never found eosinophiles in other tumors except in one case of lymphosarcoma[2] (Case XX).

Of the 108 cases 74 per cent were inflammatory and counting the cases of tuberculosis and syphilis 83.3 per cent were infectious processes.

These observations show that these cells are frequently present and probably take an active part in inflammatory lesions. Eosinophiles were found in greatest numbers in appendicitis, pyosalpynx, chronic ovarian abscess, and carcinoma. They were almost always associated with plasma cells, which were often very numerous. Polymorphonuclear neutrophiles were not numerous as a rule, but in some cases, in salpingitis especially, they were abundant.

There is a close relation between the occurrence of eosinophiles and plasma cells. In many cases (as will be hereinafter described), especially in appendicitis, the transition of plasma cells into eosinophiles was readily traced. In appendicitis the eosinophiles normally present in the stroma of the mucosa and in the lymphoid tissue are markedly increased in number and wander into the inflamed areas. In chronic appendicitis they are commonly seen in great numbers in the muscularis. In carcinoma they are sometimes seen in the blood-vessels, but even here they are closely associated with plasma cells. In a large number of cases of salpingitis, on the other hand, numbers of eosinophiles were present in the blood-vessels as well as in the tissues. In salpingitis eosinophiles were found in greatest numbers in the mucosa and in the muscularis, and but rarely in the serosa or in the lumen of the tube. There is evidence, then, that in salpingitis some of the eosinophiles in the exudation are derived from the blood-vessels. We are informed, however, by Dr. Weir, the Resident Gynaecologist, that in a number of the cases of salpingitis operated on in Dr. Robb's service showing a decided leucocytosis (of the polymorphonuclear neutrophiles) before operation, a differential count of the leucocytes always failed to show eosinophilia, even in the cases in which eosinophiles were found in large numbers in the pelvic lesions. The consideration of the bacteriology of these cases will be postponed to the end of the article.

[2] In a recently examined case of giant cell sarcoma of the mediastinal glands invading the pectoral muscles there were great numbers of eosinophiles in the tumor and in the neighboring muscle.

Description of the Eosinophilic Cells met with in the above series.

In the apparently normal tissues the stroma of the mucosa of the appendix, ileum, and stomach, for instance, by far the majority of the eosinophilic cells corresponded in all respects to those commonly found in the circulating blood. They had horseshoe-shaped, or trilobate nuclei, surrounded usually with coarse granules which stained deeply with eosin. In some of these cells, however, the granules were finer than in others. The cell outlines were often irregular. Besides these cells a few were seen with single, usually round, deeply-staining nuclei, surrounded, some by finely granular, others by coarsely granular protoplasm. Both varieties of granules stained deeply with eosin. These cells were about the same size as the large mononuclear cells with hyaline protoplasm. The nuclei of the two varieties of cells were identical in appearance, with the exception that the nuclei of the eosinophilic cells commonly stained more deeply than those of the large hyaline cells of the blood. In the second series of cases, in which eosinophilic cells were found in inflammatory and other lesions, these cells were in the main similar to those found in the apparently normal organs, with the exception that mononuclear cells were present in larger proportion in the former than in the latter.

In some of the inflammatory cases, notably in ovarian abscesses and in pyosalpinx the eosinophilic cells were very numerous in the tissues. As a rule, few polymorphonuclear neutrophilic cells were present with the eosinophiles, except in acute cases, where the former were usually very numerous, and the latter few in number. Elsewhere these two varieties of cells were not commonly seen together. In the chronic cases as a rule, and often in the acute cases, especially in ovarian abscess and pyosalpinx, the eosinophiles were associated with plasma cells, which were present in large numbers. In only a few cases were the eosinophilic cells the most numerous in the exudation.

III. Cells with Eosinophilic Granulations in Organs showing Pathological Changes in Cases coming to Autopsy.

In the ten following cases cells with eosinophilic granulations were found in the spleen, in association with chronic interstitial splenitis, and in various other organs.

Case VIII. Male, aged 60 years. Interstitial splenitis with polymorphonuclear eosinophiles in fairly large numbers in the spleen pulp; carcinoma of the pancreas and liver.

Case IX. Male, aged 45 years. Congestion of the spleen with haematoidin in the trabeculae, eosinophiles in clumps of three and four in the splenic pulp. Death from intestinal obstruction.

Case X. Female, aged 3 years. Pleuropneumonia with serous effusion, interstitial splenitis, persistent thymus, healed eczema, eosinophilic cells in the splenic pulp and in the thymus. The thymus measured 5 x 3 x 2 cm. and was of ordinary appearance on section. The spleen weighed 25 gm. and measured 7 x 5 x 2 cm. The capsule was adherent to the diaphragm over an area 1 x 1 cm. On section the consistency was increased, the Malpighian bodies and trabeculae were both well marked. The outlines of sections of the spleen were serrated, the depressions corresponding to the very thick trabeculae. Beneath the capsule there were broad and narrow bands of connective-tissue thickening. In the pulp here and there, polymorphonuclear eosinophilic cells were found in considerable numbers. In many of the smaller arteries there was an obliterative endarteritis, while the media of many was hyaline. There was no round cell infiltration.

In sections of the thymus the lobule as well as Hassal's bodies were well marked. The interlobular stroma was normal. Large numbers of polymorpho- and mononuclear cells with eosinophilic granulations were seen in the lobules, in the interlobular connective-tissue and in the blood-vessels.

Case XI. Male, aged 5 years. Bronchopneumonia with general infection with *Bacillus mucosus capsulatus;* eosinophiles in the spleen and thymus.

Sections of the spleen showed marked congestion with numerous eosinophiles in the pulp. The thymus showed marked congestion with many eosinophiles (mostly mononuclear) in the lymphoid tissue; in many places they were very numerous about the bodies of Hassal.

Case XII. A still-born child at full term, with hydrocephalus and meningocele; eosinophiles in the spleen and thymus.

Sections of spleen showed marked congestion of the vessels of the pulp in which a few polymorphonuclear eosinophiles were seen.

The thymus was much congested and showed a moderate number of eosinophiles in the lymphoid tissue.

Case XIII. Male, aged 4 months. Bronchopneumonia; malnutrition; eosinophiles in the liver, spleen, ileum, colon, thymus and lymph glands.

Sections of the liver showed a number of plasma cells and a few polymorphonuclear eosinophiles in the vessels; the spleen showed large numbers of the same cells in the pulp. The small and large intestines, the thymus and the mesenteric lymph glands showed large numbers of eosinophiles, both mononuclear and polymorphonuclear, in the lymphoid as well as in the interstitial tissues.

Case XIV. Male, aged 5 years. Burns of the third degree; chronic interstitial splenitis; eosinophiles in the liver, spleen, adrenals, thymus, mesenteric lymph glands, and gastro-intestinal tract; persistent thymus.

Sections of the spleen showed congestion and diffuse increase of fibrous tissue, with a large number of mono- and polymorphonuclear eosinophiles scattered throughout the pulp, which contained large numbers of typical plasma cells. Every stage of transition between plasma cells and eosinophiles could be made out. The liver showed marked congestion of the capillaries with cloudy swelling of the liver cells; polymorphonuclear eosinophiles were found in the capillaries of the liver and adrenals, the lymphoid tissue of the thymus showed large numbers of the same cells; the mesenteric glands showed congestion and hyperplasia with large numbers of eosinophiles in the lymphoid tissue.

Case XV. Female, aged 40 years. Streptococcus bacteriaemia following pelvic abscess; interstitial splenitis with eosinophiles in the spleen, liver and abscess wall. Sections of the spleen showed marked congestion and increase of fibrous tissue with a moderate number of mono- and polymorphonuclear cells in the pulp; a few of the same cells were present in the blood-vessels of the liver. In sections of the abscess wall there were large numbers of streptococci, numerous mononuclear and polymorphonuclear eosinophiles, plasma cells and neutrophiles.

Case XVI. Male, aged 45 years. Empyaema and lobar pneumonia; interstitial splenitis with eosinophiles in the lung and spleen.

In sections of the pneumonic area the alveoli were filled with masses of fibrillated fibrin containing polymorphonuclear neutro-

philes. In some alveoli there were large globular polypoid masses of fibrin attached to the alveolar walls by narrow bases and containing fibroblasts and capillaries. In many of the alveoli and in some of the alveolar walls numerous polymorphonuclear eosinophiles were seen. The spleen showed diffuse connective-tissue increase with a few polymorphonuclear eosinophiles and many plasma cells in the pulp.

Case XVII. Male, aged 35 years. Miliary tuberculosis of the lungs with some mononuclear eosinophiles in the granulation tissues about the tubercles; diffuse interstitial splenitis with polymorphonuclear eosinophiles in the pulp; general chronic passive congestion; malaria (tertian form). Coverslips made from the spleen showed dark pigment in the leucocytes and a number of red blood-cells containing malarial parasites of the tertian type. Sections of the left lung showed chronic interstitial pneumonia, with fibrous tubercles. The tuberculous tissue was rich in plasma cells, polymorphonuclear neutrophiles and mononuclear and polymorphonuclear eosinophiles. The spleen showed marked congestion, a large amount of haematoidin in the trabeculae, and interstitial splenitis with a large number of polymorphonuclear eosinophiles in the pulp.

Five of the foregoing cases were young children (Cases X, XI, XII, XIII, XIV) and all showed large numbers of eosinophiles in the thymus as well as in the spleen. Case XIV is of special interest as the formation of eosinophiles was in active progress, and these cells were present in increased numbers in the various organs, as well as in the tissues of the spleen, thymus (persistent), lymph glands and intestines. Besides their occurrence in the spleen in the five remaining cases, they were also found in one case in the wall of a pelvic abscess (Case XV), in one case in the exudate of lobar pneumonia (Case XVI), and in one case in tuberculous areas in the lungs (Case XVII). In two cases they were present in all the organs except the heart and lungs. Although circulatory eosinophilia has been described in malaria, as far as we have been able to learn, Case XVII is the first one in which these cells have been observed in the spleen in this disease.

In the next four cases cells with eosinophilic granulations were present in large numbers in the gastro-intestinal tract.

Case XVIII. Male, aged 51 years. Atrophic cirrhosis of the liver and gastric mucosa, with eosinophiles in the stroma of the latter. Sections of the stomach showed atrophy of the glands, and infiltration of the stroma with numerous mono- and polymorphonuclear eosinophilic cells.

Case XIX. Male, aged 34 years. Arsenic poisoning; polymorphonuclear eosinophiles in the intertubular tissue of the gastric mucosa. Sections of the stomach showed some loss of the surface epithelium and marked dilatation of the blood-vessels of the mucosa. There was no special destruction of the tubules. The intertubular tissue contained numbers of plasma cells and polymorphonuclear eosinophiles. The epithelial cells of the tubules were often separated from the basement membrane, and there was marked congestion of the submucosa.

Case XX. Male, aged 64 years. General lymphosarcoma with numerous mono- and polymorphonuclear eosinophiles in the stroma and muscularis of the small intestine. Sections of the spleen, liver, kidneys, intestines and mesenteric glands showed lymphosarcoma. Sections of the duodenum and jejunum showed loss of the superficial epithelium of the mucous membrane of some of the glands, with numbers of large bacilli (*B. aërogenes capsulatus*) in the degenerated areas. In the muscularis and to a less degree in the stroma of the mucosa, a large number of cells with eosinophilic granulations were seen. These cells were of several types, and showed distinct transition forms. In the stroma of the mucosa the cells were all of one type. They had rather large, pale nuclei, and were similar in every way to plasma cells, except for the eosinophilic granulations. There were a moderate number of plasma cells in association with the eosinophiles. In the muscularis the picture was materially different. Here the prevailing type of cell had a small, very dense eccentric nucleus, round, oval or elongated, and an irregular cell body, which conformed itself to the clefts between the muscle fibres, and consequently showed a great variety of shapes; the granulations were extremely coarse, and crowded closely together. Besides these there were a number of cells similar to the above except that the nuclei were somewhat vesicular, and contained small clumps of chromatin. These forms were the most common ones, but there were also a fairly large number of ordinary polymorphonucler eosinophiles with double,

horse-shoe, or trilobate nuclei. Besides these there was a great variety of forms which were apparently transitional between the smooth muscle cell of the intestine, and the typical, fully-formed polymorphonuclear eosinophile. There were cells with double or even trilobate nuclei, but without a trace of nuclear detail, and others whose nuclei were markedly vesicular. The eosinophiles apparently had a double origin, arising on the one hand from the plasma cells which were present in both the stroma of the mucosa and in the muscularis, and on the other, from the muscle cells. Eosinophiles were present also in the capillaries and in the small veins, but were infrequent in the larger vessels. Only two types occurred, the ordinary polymorphonuclear form, and the mononuclear form with a vesicular nucleus. The forms with dense nuclei were entirely absent from the vessels. No polymorphonuclear neutrophiles were seen in the tissues.

Case XXI. Male, aged 34 years. Extensive ulceration of the rectum, sigmoid flexure and descending colon, with polymorphonuclear eosinophilic leucocytes in the large intestine and in the spleen; taenia saginata in small intestine. There was an extensive suppurating wound on the left thigh, communicating with the sigmoid. The rectum, sigmoid and colon up to the splenic flexure were the seat of larger and smaller ulcers with granulating bases and margins. Over large areas of the intestine the mucosa was lost, the surface being covered with granulation tissue.

The spleen weighed 180 gms., and measured 12 x 6 x 4 cm. The capsule was smooth; on section the organ was dark red in color, the consistency was normal. The trabeculae were prominent, the Malpighian bodies obscure. Microscopically the trabeculae were thickened, and there was a diffuse increase of connective-tissue in the pulp, with numbers of polymorphonuclear cells with eosinophile granulations. The capillaries contained a large number of polymorphonuclear neutrophilic leucocytes. In the granulation tissue of the rectum and sigmoid, in addition to fibroblasts, plasma cells and polymorphonuclear neutrophilic leucocytes, there were numbers of cells with eosinophilic granulations.

In these four cases there were numbers of eosinophiles in gastro-intestinal lesions, and in only one case (Case XIV) were those cells found in other organs. In the case of chronic dysentery they were numerous in the very much thickened splenic pulp. In con-

nection with Case XXI it is interesting to note that in a case of chronic salpingitis and ovarian abscess, occurring in a woman with tapeworm, eosinophiles were present in great numbers in the inflammatory lesions and in the blood-vessels. Unfortunately a differential count of the leucocytes of the blood was not made.

Case XXII. Female, aged 65 years. Carcinoma of bladder and uterus with numerous eosinophiles in the stroma of the tumor; interstitial splenitis with polymorphonuclear eosinophiles in the pulp. A few polymorphonuclear eosinophiles were scattered through the splenic pulp. Sections made from various portions of the uterine tumor showed typical adeno-carcinoma with large alveoli.

In the scanty stroma and in the surrounding tissues there were large numbers of mononuclear and polymorphonuclear cells with eosinophilic granulations. These cells were especially numerous in the media of small arteries, where they lay between the muscle cells and were often much elongated.

The following case is of special interest as being the first case of chronic interstitial nephritis in the round cell infiltration of which we have been able to find cells with eosinophilic granulations; it showed transition forms between the plasma cell and the eosinophile cell.

Case XXIII. Female, aged 44 years. Chronic interstitial nephritis and splenitis with eosinophilic mono- and polymorphonuclear cells in the kidneys. Sections of the kidneys showed widespread interstitial nephritis with marked atrophy of the renal tissue, both tubular and glomerular, with fibroid interstitial growth. Among the cells in the areas of round cell-infiltration there were some large mononuclear cells with non-granular cytoplasm which stained deeply and diffusely with eosin. Besides these there were many cells with granular cytoplasm which stained deeply with eosin. The liver and spleen showed nothing of special interest.

The next case is an instance of acute suppurative nephritis engrafted on chronic arteriosclerotic nephritis. The exudation in this case was marked by the presence of large numbers of polymorphonuclear eosinophiles in association with plasma cells and polymorphonuclear neutrophiles.

Case XXIV. Male, aged 62 years. Haemorrhagic cystitis, abscess of prostate, pyelo-nephritis; chronic interstitial nephritis;

polymorphonuclear neutrophilic and eosinophilic leucocytes and plasma cells in the exudation.

Sections of the kidneys showed much the same changes. There was well-marked arteriosclerotic nephritis with atrophied hyaline and fibrous glomeruli, tubular atrophy and fibrous vessel increase. Scattered through the sections there were larger and smaller areas of abscess formation with diffuse infiltration with great areas of plasma cells and polymorphonuclear neutrophilic and eosinophilic leucocytes. The most numerous cells were the neutrophiles. The capillaries were dilated, the tubules were disorganized, and the epithelial cells were in various stages of degeneration. In the deep cortical and medullary portions there were larger and smaller areas of diffuse infiltration with plasma cells, polymorphonuclear neutrophiles and eosinophiles. These cells were seen both within and without the tubules, some tubules being enormously distended with them. Cocci, short, thin bacilli, and long and stout bacilli were found. The long thick bacilli were present in great numbers. No eosinophilic cells were found in sections of the bladder and prostate.

In the next three cases[3] eosinophilic cells were found in acute interstitial nephritis.

Case XXV. Male, aged 57 years. Acute and chronic interstitial nephritis with the presence of mono- and polymorphonuclear eosinophiles and plasma cells in the interstitial tissue, epithelioma of the bladder.

Cultures were negative. Urotropin had been administered several days before death. Sections of the kidneys showed thickening of the capsules, with thinning of the cortices, which were the seat of widespread interstitial nephritis. Most of the glomeruli had disappeared, and of those which were left some were markedly thickened, while others were hyaline. The tubules were extensively atrophied, and there was a diffuse growth of fibrous tissue, rich in cells, most of which were polymorphonuclear neutrophiles, though a number of eosinophiles were seen among them. Larger and smaller collections of eosinophiles were present in the tissue. The blood-vessels were dilated, and many of the capil-

[3] These three cases were reported in full in the American Journal of the Medical Sciences, December, 1900.

laries and small veins contained numbers of leucocytes. In many places the process was acute rather than chronic, the tissues being filled with leucocytes. A few small scattered abscesses were seen in the tissue. The medullary portion showed marked congestion, the tissue was compressed and atrophied, and here and there larger and smaller collections of small round cells were seen. In the adventitia of many of the small arteries there was marked cellular infiltration. These cells were for the most part small round cells and plasma cells, but a number of large mononuclear and smaller polymorphonuclear eosinophilic cells were seen. In the adventitia of one of the small arteries, near some typical plasma cells, and some large mononuclear cells, two very interesting cells were seen. One was the size of a large mononuclear leucocyte, which had a distinct kidney-shaped nucleus. The cell had the appearance of a typical transition cell of the blood. Next to it was a cell slightly smaller in size, which was crowded with rather fine granulations, much smaller than those of a typical eosinophile; these granulations stained very deeply with eosin. The nucleus of this cell was slightly oval, and marked by larger and smaller deeply staining chromatic masses. This cell was apparently a transition of a large mononuclear into an eosinophilic leucocyte. Large numbers of eosinophiles were scattered through the kidney and in the areas of round cell infiltration.

Case XXVI. Female, aged 30 years. Acute interstitial nephritis with mono- and polymorphonuclear eosinophilic leucocytes and plasma cells in the intertubular exudation. Tuberculosis of bronchial glands with eosinophiles in the tuberculous tissue. Prolapsus uteri, abortion, vaginal hysterectomy. Small stitch abscess containing *Staphylococcus aureus.* In the bronchial glands there were a number of areas containing giant and epithelioid cells, while in the lymph spaces and stroma there were numerous mono- and polymorphonuclear eosinophiles.

In the kidneys there were numerous areas of cellular infiltration, in many of which the glomerular capillaries were thick and congested and showed an increase of cells, some of which had eosinophilic granulations. The tubules were compressed by an accumulation of cells in the intertubular tissue. These cells were for the most part plasma cells, but a considerable number of eosinophiles were present. The latter were seen in the capillaries as

well as in the tissues. The epithelial cells of the tubules were compressed and many were swollen and granular.

Case XXVII. Female, aged 35 years. Acute interstitial nephritis with numbers of eosinophiles and plasma cells in the exudation.

Anatomical Diagnosis.—Streptococcus septicaemia following abortion; stomatitis, pharyngitis, bronchitis, bronchopneumonia, and oedema and congestion of the lungs; acute interstitial nephritis, acute splenic tumor, retained placenta. The kidneys were large; the right weighed 370 and the left 330 grammes. The capsules stripped off readily, the surfaces were smooth, pale and stained with bile pigment. On section the organs were hyperaemic and markedly oedematous and opaque. The consistency was increased. The cortices averaged 1 cm. in thickness; the glomeruli were inconspicuous; both organs were bile stained. On microscopic examination the kidneys showed marked oedema and congestion. The glomerular capillaries were dilated and contained a few polymorphonuclear eosinophiles. The capsular epithelium was swollen and granular as was the epithelium of the convoluted tubules. There were larger and smaller areas of cellular infiltration in the intertubular tissues of the cortex both near the surface and near the medulla. In many places the tubules were markedly compressed by this exudation, in which three main varieties of cells could be distinguished, viz., lymphocytes, plasma cells and polymorphonuclear cells with eosinophilic granulations. Some tubules were filled with desquamated epithelial cells and leucocytes in varying numbers. Throughout the kidneys the bloodvessels, especially the capillaries, contained large numbers of polymorphonuclear eosinophilic cells, which were most numerous near the areas of cellular infiltration. In these areas of interstitial nephritis the most numerous cells were plasma cells; next in number to these ranked the eosinophilic cells. In some places the eosinophilic cells were the most numerous cells in the exudation.

There were five cases of nephritis with eosinophiles in the renal lesions. The first (Case XXIII) was a typical case of chronic interstitial nephritis, in the cellular infiltration of which eosinophiles were found. In Case XXIV, the kidneys were the seat of a moderate degree of arteriosclerotic nephritis, and there was a double-sided acute suppurative nephritis, secondary to abscess of

the prostate, in the exudation of which besides polymorphonuclear neutrophiles there were many plasma cells and eosinophiles. Case XXV was also an example of moderate chronic nephritis with acute suppurative nephritis, secondary to chronic cystitis and epithelioma of the bladder. The eosinophiles and plasma cells were very numerous. In Cases XXVI and XXVII, there was typical acute interstitial nephritis with large numbers of eosinophiles and plasma cells in the exudation. In both cases there had been abortion and in the last case streptococcus septicaemia. The eosinophiles were so numerous that the process might with propriety be called acute eosinophilous nephritis.

Case XXVIII. Male, aged 19 years. Caseous and miliary tuberculosis with oedema of the lymph glands with the presence of large numbers of eosinophiles. Recent tubercular pleurisy and pericarditis. General infection with *Staphylococcus aureus.*

Sections of various lymph glands showed marked oedema with miliary and caseous tuberculosis. Sections of one mesenteric gland showed as follows:

Larger and smaller areas of caseation were surrounded by a reticular fibrous tissue in the meshes of which there were many cells, among which there were giant cells, epithelioid cells, plasma cells and lymphocytes. There was enormous oedema which distended the spaces of the reticular tissue as well as the lymph channels. Many of the lymph channels, especially in the centre of the gland, were crowded with cells, most of which were plasma cells, hyaline leucocytes and lymphocytes, with relatively few polymorphous nuclear cells. In many plasma cells nuclear figures were seen. In the widely distended reticulum, there were relatively few cells, most of which were very large oval cells, some with densely staining and some with vesicular nuclei, surrounded by a large amount of finely granular protoplasm. The nuclei were often eccentric and sometimes reniform. The granules were not eosinophilic, but the cells were markedly phagocytic, and often contained plasma cells, lymphocytes and even eosinophiles. The germinal centres were increased in size, the most numerous cell being the plasma cell. There were also many eosinophiles. Nearly everywhere in the tissue there were variable and often large numbers of coarsely granular eosinophiles, some with polymorphous nuclei but most with a single, rather deeply-staining nucleus.

Many cells with nuclei similar to those of plasma cells surrounded with fine eosinophilic granulations were seen. The blood-vessels were not congested and showed no increase of leucocytes.

Case XXIX. Male, aged 17 years. General miliary tuberculosis with mono- and polymorphonuclear eosinophiles in the mesenteric and retroperitoneal lymph glands, which were large, soft and oedematous.

Sections from these glands showed typical miliary and conglomerate tubercles containing many giant cells and often showing caseation. In many places there was marked oedema, increase of the cells of the germinal centres and dilatation of the lymph channels, with the presence of large numbers of cells in the stroma and in the channels. These cells were chiefly plasma cells but there were also present a number of mononuclear eosinophiles with eccentric nuclei, closely resembling plasma cells in all respects except eosinophilic granulations. A few ordinary polymorphonuclear eosinophiles were also present.

These two cases are of great interest, for with the eight cases of tuberculosis with eosinophilic infiltration met with in our operative material, and the lymph gland tuberculosis of Case XXVI and the lung tuberculosis in Case XVII, they make twelve instances in which we have observed eosinophiles in tubercular lesions. The development of eosinophiles from plasma cells and hyaline leucocytes could be readily traced in the tuberculous lymph glands.

Case XXX. Male, aged 49 years. Eosinophiles in a wall of a liver abscess secondary to pneumonia and empyaema. General streptococcus infection. Sections of the wall of the hepatic abscess showed marked congestion of the blood-vessels with compression of the liver cells. The abscess wall was infiltrated with polymorphonuclear neutrophiles, plasma cells and coarsely granular eosinophiles.

This is the third case in which we have found eosinophiles in the liver. Case XIV showed them in the portal spaces in a child dead of burns; while in Case XV they were found in the vessels of angioma of the liver of a woman with pelvic abscess.

Case XXXI. This case has already been published by one of us (Howard).[4] For the clinical history and autopsy we are in-

[4] Howard, W. T., Jr. Philadelphia Medical Journal, 1899, vol. IV, p. 1085.

debted to the kindness of Dr. Hoover. Female, aged 35 years, was ill for three weeks with diarrhoea and vomiting and complained of pain in the abdomen and the muscles of the extremities. Coverslip preparations of the blood stained with Ehrlich's triacid stain, on examination by Dr. Hoover, showed a slight leucocytosis, without however an increase in the number of eosinophiles. Although Dr. Hoover did not make a differential count, he is confident that there was no circulatory eosinophilia. A piece of the extensor quadratus of this case was excised and showed large numbers of *Trichina spiralis*. Death occurred at the end of three weeks from the onset.

Anatomical Diagnosis.—General infection of the voluntary muscles with *Trichina spiralis;* acute yellow atrophy of the liver; infarction of the spleen; fatty degeneration of the heart and kidneys; congestion of the lungs and intestines.

Cultures and coverslip preparations made from the various organs showed no bacteria. Teased preparations of the tongue, the diaphragm, quadratus lumborum, psoas, and quadriceps femoris muscles showed large numbers of actively motile trichinae. No trichinae were found in the intestinal contents.

Sections of the heart showed congestion of the capillaries and small veins—in some of the latter there were small accumulations of large and small mononuclear leucocytes; no cells with eosinophilic granulations were found. Larger and smaller areas of cellular infiltration were seen between some of the muscle fibres, the cells consisting of lymphocytes, plasma cells, a few polymorphonuclear neutrophilic leucocytes, and a number of both polymorpho- and mononuclear cells with marked eosinophilic granulations.

In the lungs there was found marked oedema with congestion. In the peribronchial tissue and in the lymph spaces, but never in the small blood-vessels a few polymorpho- and mononuclear eosinophiles were found. The larger pulmonary veins, however, contained numbers of these cells.

In sections of the liver, it was often impossible to recognize the tissue. There was widespread fatty degeneration and nuclear fragmentation. In some places the liver cells were small, shrunken, very granular, and stained intensely with eosin; in other places they were swollen, and contained large and small fat drops. The

blood-vessels showed no special changes, but many capillaries contained numerous neutrophiles, but no eosinophiles.

The spleen showed congestion, with thickening of capsule, trabeculae and pulp, the latter containing many polymorphonuclear eosinophiles. The kidneys showed congestion and oedema, with cloudy swelling of the epithelium of the convoluted tubules.

In the stomach and large and small intestines there were a number of polymorpho- and mononuclear eosinophiles in the interglandular stroma.

In sections of the tongue and diaphragm there were large numbers of trichinae of varying size situated in the muscle fibres. The trichinae were usually single, but in many places two and even three were seen in the same cyst. The trichinae were situated in the muscle fibres, and were surrounded by a hyaline capsule of varying thickness. In many places, especially at the poles of the cysts, there was very active multiplication of muscle nuclei, which were for the most part long, vesicular, and often irregularly constricted. Muscle fibres containing trichinae, both near to and at a distance from the latter were swollen, had lost their striations and showed large and small finely granular amorphous areas of degeneration which stained deeply with eosin. About some trichinae there was little cellular reaction, while about others great numbers of cells were seen. In many places there was marked proliferation of muscle nuclei in fibres in which no trichinae were to be found.

The process was evidently an acute one. There was no evidence of calcification. In the cellular reaction about the trichinous areas the following varieties of cells could be distinguished:

I. Cells in every way like plasma cells, having a single, round, or oval, somewhat pale nucleus, containing larger and smaller chromatin masses, surrounded by a varying amount of homogeneous cytoplasm which stained faintly with eosin. In some of these cells the nucleus was centrally placed, but in most it was eccentric. In shape these cells were round or long oval; occasionally they were very much elongated (amoeboid movement?). They were the most numerous cells present.

II. Cells with nuclei of the same size and appearance as No. I, surrounded by homogeneous cytoplasm which stained deeply with eosin. These cells were fairly numerous.

III. Cells with nuclei similar to Nos. I and II, surrounded by cytoplasm containing very fine eosinophilic granulations.

IV. Cells of the size of large mononuclear leucocytes, with rather deeply staining nuclei, surrounded by either finely granular or coarsely granular deeply staining eosinophilic granulations. These cells were quite numerous.

V. Polymorphonuclear cells, with reniform horseshoe-shaped, or trilobate nuclei, and cytoplasm containing either finely or trilobate nuclei, and cytoplasm containing either finely or coarsely granular eosinophilic granulations. These cells were numerous, and were the exact counterpart of the polymorphonuclear eosinophilic cell of the blood.

VI. A variable number of small round cells with single deeply-staining nuclei, surrounded by a narrow rim of granular protoplasm. These were typical lymphocytes.

VII. Cells of varying size, usually very large, containing large, elongated, vesicular nuclei. These cells were very numerous in places, and were evidently proliferating muscle cells.

VIII. A few typical fibro-blasts.

IX. A few giant cells with from four to six nuclei, and homogeneous non-granular protoplasm.

X. A few neutrophilic polymorphonuclear leucocytes.

In some places, especially at the margins of the areas of cellular infiltration, there were seen rows of polymorpho- and mononuclear cells with eccentric nuclei, and many with fine or coarse eosinophilic granulations.

The blood-vessels were dilated but showed no increase of leucocytes in the small veins, but in some capillaries there were a considerable number of mononuclear cells.

Careful search failed to discover transition of polymorphonuclear neutrophilic cells into eosinophiles. There was absolutely no evidence of this mode of origin for the eosinophilic cells.

The most numerous and apparently the most important cell in the reaction in this case was the plasma cell. The cells with eosinophilic granulations were much less numerous than the plasma cells. The development of the former from the latter could be readily and easily traced as follows: The homogeneous protoplasm of the plasma cell becomes first faintly and then strongly eosinophilic. In the next stage, fine, and later coarser eosino-

philic granulations develop, producing typical mononuclear eosinophiles. Some of these latter develop polymorphous nuclei. With the development of granulations the plasma cells often increase in size. The size of the eosinophilic cells varies, however, within rather wide limits. In this case at least, it seems certain that the eosinophiles were formed in the areas of cellular reaction about the muscle trichinae, and were not brought there from a distance by the blood-vessels being drawn by chemotactic substances thrown out by the parasites, or furnished by the degenerating muscle. The substances present, whatever their nature, exerted a chemotactic action on the plasma cells.

The presence of increased numbers of eosinophiles in the stroma of the mucosa of the stomach and intestine is probably to be explained by the recent presence of trichinae in the intestine and intestinal wall. Here too the eosinophiles probably had their origin in plasma cells. The course of the disease in this case was more acute than in the cases of Brown,[5] Gwyn,[6] Atkinson[7] and Stump[8] and this fact probably explains the absence of circulatory eosinophilia. Had the individual lived longer, or the infection been less severe, it is probable that eosinophiles would have made their way into the blood. It is recognized that the presence of a circulatory eosinophilia during life cannot be positively denied in the absence of a differential count, on the strength of Dr. Hoover's impression from the examination of stained preparations. If, however, the eosinophiles were much increased in the circulating blood during life, it would be strange to find the percentage normal in differential counts of preparations made from the blood of the organs after they reached the laboratory.

This case demonstrates among other things that trichinosis may exist and run a fatal course apparently without increase of eosinophiles in the circulating blood, and that a high grade of eosinophilia, such as was present in the cases of Brown, Gwyn, Atkinson and Stump (42, 49, 68.2, 72, 58.5 and 52 per cent) speaks for a

[5] Brown, T. R. Bulletin of the Johns Hopkins Hospital, 1887, vol. VIII. Journal of Experimental Medicine, 1898.

[6] Gwyn, N. B. Centralbl. f. Bakteriologie, 1899, Band xxv, S. 746.

[7] Atkinson. Philadelphia Medical Journal, June 3, 1899.

[8] Stump. Philadelphia Medical Journal, June 17, 1899.

good prognosis and indicates that the organism is reacting well to the poison of the trichinae. The marked degeneration of the liver and kidneys of our case shows that the tissues were acted upon by a powerful poison. Brown's observation that the eosinophiles in the muscle in trichinosis are formed in the lesions and are not attracted there by chemotactic substances, is supported by the findings in this case. We believe that trichinae or a poison or poisons secreted by them have a positive chemotaxis for hyaline leucocytes, plasma cells, and polymorphonuclear leucocytes and that for some unknown reason certain of the first two varieties of cells develop eosinophilic granulations.

Histogenesis of Eosinophilic Cells.

There are several theories in regard to the histogenesis of eosinophilic cells and in support of each theory a certain amount of evidence has been brought forward. These theories and their main supporters are as follows:

I. From polymorphonuclear neutrophilic leucocytes by a kind of ripening process, Max Schultze,[9] Gulland,[10] Zappert,[11] Brown[12] and others.

II. From eosinophilic myelocytes in the bone-marrow only, Ehrlich.[13]

III. Division of pre-existing cells of the same kind, by mitosis, Müller und Rieder,[14] and Van der Stricht;[15] by amitosis, Rénaut,[16] Denys[17] and Arnold; Gulland,[18] who has exhaustively studied the leucocytes of many species of animals thinks that all forms of leucocytes give rise on division to lymphocytes, but that occasionally on the division of eosinophiles the daughter-cells may contain a few eosinophilic granulations.

[9] Schultze, Max. Arch. f. Mikroskop. Anat. 1865, I.
[10] Gulland. Journal of Physiology, 1895–6, Vol. xix.
[11] Zappert. Zeitschrift f. Klin. Med. 1893, Bd. xxiii.
[12] Brown. Loc. cit.
[13] Ehrlich and Lazarus. Die Anemie. Wien, 1898.
[14] Müller und Rieder. Deutsch. Arch. f. Klin. Med., 1891–2, Vol. xlviii.
[15] Van der Stricht. Quoted by Brown, loc. cit.
[16] Rénaut. Quoted by Brown, loc. cit.
[17] Denys. Quoted by Brown, loc. cit.
[18] Gulland. Loc. cit.

IV. From the connective-tissue of various parts of the body, Gollasch,[19] Neusser,[20] Weiss[21] and others. Kanthack and Hardy[22] found these cells in numbers in the caelomic cavity and connective-tissues of animals.

V. Occurring as incompletely developed erythrocytes, derived from haematoblasts, Przewaski.[23]

VI. From the engulfing of haemoglobin of haematoblasts by leucocytes, Sacharoff,[24] who thinks that the granules are connected with the dispersion of haematin and that the intense coloration of eosinophilic granulations is due to the greater thickness of their iron-bearing paranuclein. According to Sacharoff, bacteria taken up by leucocytes may furnish eosinophilic material, their nuclein being changed into eosinophilic paranuclein. Klein[25] thinks that eosinophiles are formed from other leucocytes by the taking up of iron derived from red blood cells.

VII. From lymphocytes by transition, Pappenheim.[26]

It is neither impossible nor indeed improbable that these cells may have their origin in any of these several ways.

Ehrlich and Lazarus strongly combat the idea of the local formation of eosinophiles.

While not denying that these cells may have their origin in many ways, in the study of our rather large material, we have never been able to trace any one of these modes of origin (except from eosinophilic myelocytes). We have been struck on the other hand with the great frequency with which the origin of these cells can be traced from the hyaline leucocyte, and especially from the plasma cell. In case after case, in organ after organ, and especially in the lymphoid tissues (the thymus, lymph glands, the spleen, and the bone-marrow), in the gastro-intestinal mucosa (gastritis, lympho-sarcoma, colitis, and appendicitis), in

[19] Gollasch. Fortschritte d. Med., 1899, Bd. vii.

[20] Neusser. Wien. klin. Wochenschr., 1892, Bd. xli, p. 64.

[21] Weiss. Quoted by Brown, also by H. F. Muller. Centralbl. f. allgem. Path. u. path. Anatomie.

[22] Kanthack and Hardy. Journal of Physiology, 1894–5, Vol. xvii.

[23] Przewaski. Centralbl. f. allg. Path. und path. Anat., 1896, Bd. vii, S. 177.

[24] Sacharoff. Centralbl. f. Bakteriologie, 1897, Bd. xxi, S. 265.

[25] Klein, S. Centralbl. f. Innere Med., 1899, Bd. L, S. 28.

[26] Pappenheim. Virchow's Archiv., 1899, Bd. 157, p. 71.

exudations rich in lymphocytes, hyaline leucocytes and plasma cells (acute and chronic nephritis, salpingitis and ovarian abscess, etc.) and in various other processes, we have observed the transition of both these varieties of cells into eosinophiles.

As already pointed out, the hyaline, or better as Kanthack and Hardy aptly term it, the "ground glass" cytoplasm of the hyaline cell or the plasma cell (for the latter often comes from the former) stains more deeply with eosin than its neighbors. In other cells with clear nuclei, which are often eccentric, there are fine granules which stain deeply with eosin. Other cells with similar nuclei have more coarsely granular and others still very coarsely granular cytoplasm. With the development of the eosinophilic granules the cells usually, but by no means always, increase in size. With the development of the granules the nuclei become less vesicular, and the nuclear chromatin more diffuse. Many coarsely granular as well as finely granular mononuclear eosinophiles were seen, but always a large proportion of the mononuclear cells develop polymorphous nuclei. We have been struck with the large proportion of mononuclear eosinophiles present in some cases. If the idea of Gulland and others that the change in the shape of the nucleus of the leucocyte is dependent largely upon the motion of the cell is correct, the above fact is another argument in favor of the origin of eosinophiles from plasma cells. In size the eosinophile in the tissues varies within rather wide limits, from the size of a small plasma cell, scarcely larger than a lymphocyte, to that of the typical eosinophile of the blood.[27]

In Case XX we observed appearances which we cannot interpret otherwise than that they represent the development of coarsely granular eosinophiles from smooth muscle cells. In the same case there were also many examples of the plasma cell origin of these cells.

Character of Eosinophilic Granulations.

We have nothing to add to the knowledge of the character and composition of these granules. For the literature of the subject

[27] A good description with a full account of the plasma cell will be found in Councilman's article on Acute Interstitial Nephritis, Journal of Experimental Medicine, 1898, vol. III, p. 393. See also Marschalko's Zur Plasmazellenfrage, Centralbl. f. Allgem. Pathologie und path. Anatomie. 1899, Bd. x, S. 851.

the reader is referred to Brown's recent article in the Journal of Experimental Medicine (loc. cit.).

First mistaken for fat, which was disproved by Ehrlich,[28] who first suggested that they represented a nutritive reserve formed by the cell, these granules have been considered in turn non-proteid (Schwarze);[29] proteid (Zappert);[30] haemoglobin or its derivatives (Przewaski[31] and others); nucleo-albumin (Sherrington);[32] and secretory granules of a defensive nature (Hankin),[33] Kanthack and Hardy.[34] Gulland,[35] however, insists that they are not products of the metabolic activity of the cell imbedded in the protoplasm, but that they represent an altered condition of the microsomes, form a part of the cytomitoma, and are therefore, plastic and not paraplastic, as is generally believed. Gulland thinks that they are concerned in the amoeboid activity of the cell. As previously stated we were unable to demonstrate the presence of iron in the granules of eosinophiles in hardened tissues.

Presence of Eosinophiles in Normal Organs.

Beside the blood, coarsely granular eosinophiles are normally found in various tissues of the human body, the spleen, thymus (earliest mention probably by J. Schaffer[36]), the lymph glands, bone-marrow, the gastro-intestinal tract (especially the stroma of the mucosa), in the kidneys and liver, and in various connective tissues. They are found in the same locations in various lower animals. They form from 25 to 40 per cent of the wandering cells in the peritoneal cavity in the guinea-pig, and from 30 to 50 per cent in rabbits (Kanthack and Hardy). In these animals they are also numerous in the subcutaneous tissue. We have found these cells but rarely in apparently normal organs of adults—in

[28] Ehrlich. Loc. cit. S. 86, and in other writings.

[29] Schwarze. Ueber eosinophile Zellen. Inaug. Diss. Berlin, 1880.

[30] Zappert. Loc. cit.

[31] Przewaski. Loc. cit.

[32] Sherrington. Proceed. Royal. Soc. Lond., 1894, vol. lv. Also quoted by Brown.

[33] Hankin. Centralbl. f. Bakteriologie, 1892, Bd. xi.

[34] Kanthack and Hardy. Loc. cit.

[35] Gulland. Loc. cit.

[36] Schaffer J. Centralbl. f. d. Med. Wissensch., 1891, nos. 22 u. 23.

ten cases in the appendix, once in the Fallopian tube, and once in the gastro-intestinal mucosa.[37] Heidenhain found them constantly present in the intestinal mucosa of dogs, in which their numbers were greatly increased after fasting and a dose of magnesium sulphate. Eosinophiles were not uncommonly found in various organs in children dying both with and without septicaemia. We have also been able to confirm the observations of those who have described eosinophiles in numbers in the blood and tissues of the foetus.

Presence of Eosinophiles in Inflammatory and other Lesions.

With a few notable exceptions coarsely granular eosinophiles have not been described in inflammatory reactions and in infectious granulomata. They have been found in gonorrhoeal pus in numbers by Gollasch[38] and others, in the sputum in bronchial asthma by Gollasch,[39] Leyden[40] and others, in the sputum in bronchitis by Leyden,[41] Teichmüller, Grünwald[42] and others; in the skin in lymphoderma perniciosa by Weiss[43] and in leprosy by Jadassohn;[44] in the blisters of pemphigus by Neusser[45] and others; in Dühring's disease by Leredde and Perrin;[46] in blisters produced artificially by Bettman[47] and by Kanthack and Hardy; in hemorrhagic pleurisy by Klein[48] and Harmasen.[49] Gronven[50] found

[37] On further study we find eosinophiles constantly present in the stroma of the mucosa and often in the lymphoid tissue of both the normal and inflamed appendix.

[38] Gollasch. Loc. cit.

[39] Gollasch. Loc. cit.

[40] Leyden. Deutsch. Med. Wochenschr., 1891, Bd. xvii, S. 1085.

[41] Leyden. Loc. cit.

[42] Grünwald. Virchow's Archiv. 1899. Bd. 158, S. 289.

[43] Weiss, Jul. Jahrb. f. Kinderheilkunde, N. F. Bd. 35, quoted by H. F. Müller, Centralbl. f. allg. Path. u. path. Anat., 1893, Bd. iv, S. 539.

[44] Jadassohn. Verhandl. d. deutsch. dermat. Gesellsch. ii u. iii, quoted by H. F. Müller, loc. cit.

[45] Neusser. Wiener Med. Wochenschr., 1892, 5 Jahr., S. 41.

[46] Leredde und Perrin. Ann. de dermat. et Syph., iii ser. Tome vi, p. 281.

[47] Bettman. Münchener Med. Wochenschr., 1898, no. 39.

[48] Klein. Loc. cit.

[49] Harmasen. Quoted by Klein.

[50] Gronven. Inaug. Dissertation, Bonn, 1895.

eosinophiles in the false membrane of diphtheria in two cases, in pneumonia in diphtheria in one case, in a tumor of the larynx and in the bronchial glands in two cases. Przewaski[51] found large numbers of eosinophiles in carcinoma of the cervix uteri in four cases, while Fledbausch[52] observed them in variable numbers in epitheliomata, carcinomata and lymphosarcomata. They were most numerous about inflammatory and necrotic areas. Grünwald[53] observed coarsely granular eosinophiles in the sputum in one case each of asthma, fetid bronchitis and phthisis and in four nasal polyps. They were absent in pneumonia, pleurisy, pericarditis, gonorrhoea, abscess of the breast and the ear and in chancre. Grünwald describes cells with fine, scattered granules which are eosinophilic to a lesser degree than those of the ordinary eosinophiles, and to these cells which he found in numbers in sputum and other discharges he gives the name "hypoeosinophiles." T. R. Brown[54] and one of us (Howard[55]) found large numbers of eosinophiles in the reaction about trichinae in human muscle. In our material derived from operation eosinophiles occurred in 13.09 per cent of the cases, of which over 74 per cent were inflammatory, and including the cases of syphilis and tuberculosis 83.8 per cent were infectious processes.

To recapitulate: we have found both mono- and polymorphonuclear eosinophiles in the gastro-intestinal tract, the spleen, thymus, appendix and Fallopian tubes in apparently normal organs and in the following pathological conditions: abscess of Bartholin's gland, angioma of the liver, appendicitis, in carcinomata of the arm, the bladder, and of the uterus and scrotum, in corpus luteum cysts, in chronic cystitis, in dysentery, in endometritis, in epithelioma of the vagina, face, and of lymph glands, in atrophic gastritis and arsenical gastritis, in interstitial splenitis, in gonorrhoeal lymphadenitis, in lymphosarcoma, in nasal polyps, in acute and chronic interstitial nephritis, in suppurative nephritis, in omentitis, in pelvic abscesses and in a pilonidal abscess, in oophoritis and peri-

[51] Przewaski. Loc. cit.

[52] Fledbausch. Virchow's Archiv. 1900. Bd. 161.

[53] Grünwald. Loc. cit.

[54] Brown, T. R. Loc. cit.

[55] Howard. Loc. cit.

oophoritis, in lobar pneumonia, in proctitis, in acute and chronic salpingitis, in trichinosis, in the spleen in malaria, and in tuberculosis of the muscles, of the skin and of the lungs, bone, ureter and lymph glands, and in syphilis of the skin.

We have failed after careful search to find them in organizing blood-clots, haemorrhages into tissue, haemorrhagic infarcts, organizing thrombi of the heart and blood-vessels, organizing corpora lutea, and a number of cases of abortion remnants containing blood.

Modes of Development and Causes of Increase in the Number of Eosinophiles in the Blood.

In the light of our present knowledge, it is clear that these occur in at least two ways: (a) When an abnormally large number of eosinophiles are needed in a particular part of the body, i. e., when substances possessing positive chemotaxis for these cells are present in a part they are drawn from the haematopoietic organs, and reach the part by means of the lymph and blood channels; thus appearing in the blood in increased numbers. (b) When under proper stimulation, numbers of eosinophiles have been formed in a part, and after the need for them is past, and for other reasons not yet understood, they make their way into the lymph and blood-vessels, producing eosinophilia.

A third explanation, one for which, however, there does not seem to be any positive evidence, is that circulatory eosiniphilia may develop by the transition of certain forms of leucocytes into eosinophiles in the circulating blood. A priori, there is no reason against this mode of origin. If these cells develop from other leucocytes (hyaline cells, plasma cells, lymphocytes, and polymorphonuclear neutrophiles) in the tissues, why not in the blood as well?

In our cases (consult Groups II and III), especially the inflammatory cases, two sources for the eosinophiles in the lesions were demonstrated, i. e., the blood-vessels, and transition from plasma cells and hyaline leucocytes in the lesions. In many cases the two processes could be traced in the same lesion.

Kanthack and Hardy[56] have shown that these cells are the first

[56] Kanthack and Hardy. Loc. cit.

to wander into capillary tubes, and into Ziegler's plates containing bacteria and other irritants in the peritoneal cavity and subcutaneous tissues of rabbits and other animals. They also showed that these cells are formed or accumulate very rapidly in the connective-tissues of animals after injury. We found the eosinophiles the most numerous cells present in multiple renal abscesses occurring in a rabbit after inoculation with *Staphylococcus aureus.* T. R. Brown and Klein are among the authors who have brought out the fact that eosinophiles are formed in the lesions. Klein thinks that polymorphonuclear neutrophilic leucocytes attracted to a place and left to their fate become eosinophiles.

Leredde[57] believes that the pemphigus foliaceus is due to the excretion of eosinophiles by the skin, and concludes that the skin affection is a secondary matter. He regards the affection as essentially one of the blood due to the reaction of the haematopoietic organs, especially the bone-marrow, under the influence of multiple intoxications. This conception is quite the opposite of Neusser's view. It is difficult to conceive of the *excretion* of eosinophiles by the skin. It is much more in accordance with our knowledge to think that these cells are attracted to the foci of disease, the haematopoietic organs being stimulated to their production, or that they were formed in the lesions.

Our own conception is that in many conditions the formation of eosinophiles in the regular haematopoietic centres is stimulated by a variety of substances, many of which also have the property of attracting these cells. In other conditions other forms of leucocytes, but especially hyaline leucocytes and plasma cells and possibly certain tissue cells, develop eosinophilic granulations in various lesions. We have evidence that these two processes may occur together in the same case.

Why are eosinophiles attracted to or formed in inflamed areas and in other lesions?

Müller[58] thinks it will be found that both asthma and pemphigus are caused by substances (bacterial?) which have a positive chemotaxis for eosinophiles, while Neusser[59] believes that eosino-

[57] Leredde. Ann. de dermat. et Syph. III n. ser. Tome x, p. 355.

[58] Müller, H. F. Loc cit.

[59] Neusser. Loc. cit.

philes may be derived from the tissue cells on stimulation of the sympathetic nerves, in the same way that granules are secreted in the mucous cells of the salivary glands of the dog after stimulation of the sympathetic nerve of the gland. According to this view the bronchial mucous membranes in asthma and the skin in pemphigus, play the part of blood-forming organs in secreting eosinophilic granulations.

Goldman,[60] Jadassohn,[61] H. F. Müller,[62] hold that there are certain substances which possess a positive chemotaxis for eosinophiles. Ehrlich and Lazarus,[63] adopting this view, state that this property is possessed chiefly by the products of the degeneration of epithelial and epithelioid cells. In this way they explain the common occurrence of eosinophilia in skin diseases, in atrophic lesions of the gastric, intestinal and bronchial mucous membranes, in the neighborhood of carcinoma and in lupus after tuberculin injection. They think that the mucin or mucin-like bodies in mucous polyps of the nares, must attract these cells.

For most forms of eosinophilia the direct cause, according to these authors, is to be sought for in tissue destruction and its products. They also suggest that the eosinophilia of the various forms of helminthiasis is due to the positive chemotaxis exerted on these cells by poison secreted by the parasites.

As we have already stated, Kanthack and Hardy observed that various substances, including silver nitrate, turpentine, and copper, *B. ramosus*, *B. cholerae*, *B. pyocyaneus*, and *B. anthracis* in animals and liquor epipoeticus upon the human arm, all possessed a strong chemotaxis for eosinophiles. In our operative material bacteriological examinations were negative in many cases, especially in salpingitis and ovarian abscess. In some of these cases a more or less clear history of gonorrhoea was obtained. Taking the operative and autopsy material together, the following varieties of bacteria were found in processes marked by the presence of eosinophiles: *Streptococcus pyogenes*, *Staphylococcus pyogenes aureus* and *albus*, *Gonococcus*, *Pneumococcus*, *B. coli communis*,

[60] Goldman. Centralbl. f. allgem. Path. u. path. Anat. 1893, Bd. iii, S. 665.

[61] Jadassohn. Loc. cit.

[62] Müller, H. F. Loc. cit.

[63] Ehrlich u. Lazarus. Loc. cit. S. 113 and 114.

B. mucosus capsulatus, *B. aërogenes capsulatus* (once in the kidney), *B. tuberculosis*. To these may be added the two cases of infection with animal parasites, malaria and trichinosis.

In the autopsy series the *Streptococcus* was the organism most frequently found.

That coarsely granular eosinophiles play an important part in many inflammatory, and a variety of other, processes, is shown by the cases reported in this article as well as by the experiences of other observers. Our experience agrees with that of Metschnikoff [84] and Kanthack and Hardy who state that these cells never act as phagocytes. We have never seen them near bacteria, but have found them in great numbers about trichinae, without, however, ever invading the cysts.

We have not been able to confirm the statement of Kanthack and Hardy, that these cells apply themselves to bacteria in exudations and use up their granules in fighting them.

SUMMARY.

In the routine examination of 825 specimens removed by operation, coarsely granular eosinophiles were found in the normal appendix in 10 cases, and in the normal Fallopian tube in one case.

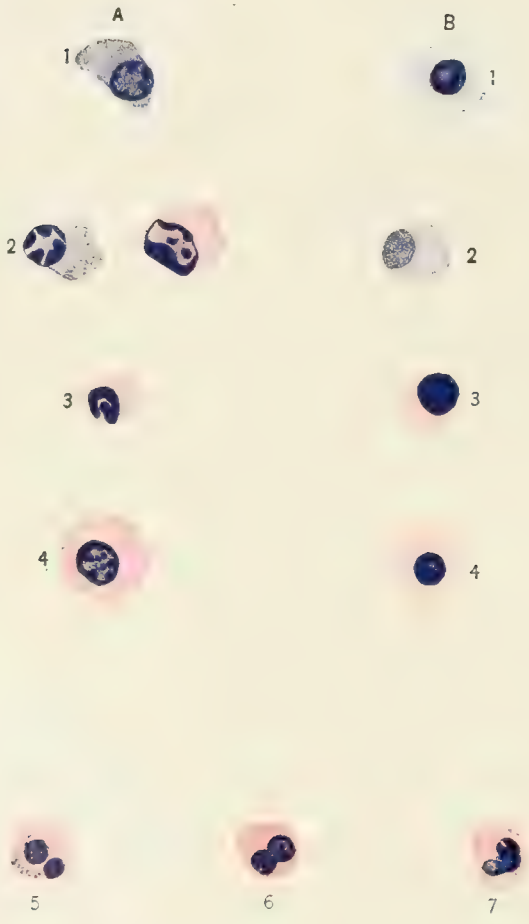
These cells occurred in larger or smaller numbers in the tissues or blood-vessels, or both, in 108 cases, or in 13.09 per cent; 83.3 per cent of these lesions were infectious in origin.

In seven cases (one adult and the rest children), four of which died of infectious processes, eosinophiles were present in apparently normal organs.

In 120 consecutive autopsies 27 cases showed larger or smaller numbers of eosinophiles in various organs showing pathological changes. In this series they occurred in the spleen in chronic interstitial splenitis in 11 cases, in the thymus in 5 cases, in lymph glands in 3 cases, in the stomach in 3 cases, in the intestine in 2 cases, in the kidney in 5 cases, in the lungs in 3 cases, in the liver in 3 cases, in the heart in 1 case, in the skeletal muscles in trichinosis in 1 case.

In some cases these cells were brought to the part by the blood-

[84] Metschnikoff. Pathologie comparée de l'Inflammation p. 136.



D. F. Whitcomb, Sc.

vessels, and in others they were formed in the lesions, while in still other cases their presence was to be accounted for in both of these ways.

In a large number of cases the development of coarsely granular eosinophiles was traced from plasma cells and in some cases from hyaline leucocytes.

DESCRIPTION OF PLATE.

The sections from which the drawings were made were hardened in Zenker's fluid and stained with haematoxylin and eosin or with eosin and methylene blue. The figures were drawn with the aid of a Zeiss camera lucida with a Reichert 1–12 oil immersion lens and 4 ocular.

Figures A 2, 3 and 4 show the development of eosinophiles from the plasma cells; figures B 2, 3 and 4 show transitions between the hyaline leucocyte and the eosinophile; figures 5, 6 and 7 represent eosinophiles which may have had either of the above modes of origin.

A. 1. Typical plasma with clear nucleus eccentrically placed, cytoplasm unstained by eosin (basophilic).
   2. Plasma cell the cytoplasm of which stains diffusely pink with eosin (acidophilic).
   3. Plasma cell with eccentric nucleus and cytoplasm with fine eosinophilic granulations.
   4. Large cell with a round nucleus similar to that of the plasma cell and with coarse eosinophilic granulations of its cytoplasm.

B. 1. Large mononuclear leucocyte with centrally placed deeply staining nucleus and hyaline faintly basophilic cytoplasm.
   2. Large mononuclear leucocyte with deeply staining eccentrically placed nucleus and cytoplasm which stains diffusely pink with eosin (acidophilic).
   3. Cell with nucleus similar to 2, but with numerous fine eosinophilic granulations of its cytoplasm.
   4. Cell with round deeply staining nucleus and large scattered eosinophilic granulations of its cytoplasm.

Figures 5, 6 and 7 represent polymorphonuclear cells with varying numbers of coarse eosinophilic granulations and which apparently may have developed from either plasma cells or large mononuclear leucocytes.

Figures A 1, 2, 3 and figure 6 represent cells from the muscle lesions in trichinosis (case XXXI), Figures B 1, 2, 3 and 4 as well as figures 5 and 7 are drawn from cells in an oedematous tubercular lymph gland (case XXVIII).

PLACENTAL TRANSMISSION, WITH REPORT OF A CASE DURING TYPHOID FEVER.

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During the past year an opportunity has been afforded to study two cases of typhoid fever during pregnancy. As the number of cases is very small in which fairly complete data are available, it has been thought advisable to report our cases together with a summary of the literature. To these two cases a third has been added in which the observation as to the Widal reaction alone was made. The cases are as follows:

CASE I.—J. B. Negress. Age 23 years, admitted Nov. 16, 1900, on the eighth day of typhoid fever, complaining of headache, and pain in the limbs.

Family History.—Mother and one aunt died of "lung trouble."

Past History.—Patient has always been well and strong. Had "scarlatina" in childhood. Menstruation regular. She does not remember the date of her last period, but thinks she is three months pregnant. She has had two children, no miscarriages.

Present Illness.—For two or three weeks she has been complaining of headache and general malaise. One week ago the pains became severe in her back and limbs, from which time the onset of the disease is dated. She took to bed on November 13th. She has had no herpes, chills, nausea, nor diarrhœa.

Examination on admission.—Patient in bed in dorsal decubitus. She is a well-nourished mulatto and appears to be very sick. The color of her skin and mucous membranes is good. The tongue is coated and tremulous. The eyelids are puffed and swollen. The lungs are practically negative. A soft systolic murmur is heard at the apex of the heart. The pulse is somewhat irregular

and of small volume and low tension. Temperature is 99.8°, pulse 112, and respiration 28. The abdomen is distended. There are no rose-spots. The spleen is easily palpated. The fundus of the uterus can be felt just above the symphysis. There is no abdominal tenderness.

The patient complained of some abdominal pain up to the twelfth day, November 20th, when she aborted. It was possible to thoroughly cleanse the perineum, and to receive the fœtus in sterile towels. The secundines resisted expression, and they were allowed to remain in the uterus for twelve hours. The morning of abortion the blood count was as follows: Red blood cells, 5,480,000, white cells, 7000, hæmoglobin, 65%.

The secundines were removed under chloroform anæsthesia on November 21st. The patient bled profusely, losing about 900 cc. and it was necessary to pack the uterus. Before the operation the temperature was 103.4°, and the pulse 88. Immediately after operation the pulse was 112, and of small volume and tension. Two hours later the patient shook with a chill and sweated profusely. Thereafter the temperature and pulse fell gradually, until at 12 p. m., twelve hours after operation, the temperature was 95°, pulse 44 and respiration 20. The extremities were cold up to the knees and elbows, and the skin of the body clammy and moist. The mind was clear. There were no abdominal symptoms, except general tenderness. The abdominal walls were everywhere soft and lax, and there was no nausea nor vomiting, occasional hiccough alone was noted. After vigorous stimulation, pulse and temperature rose as gradually as they had fallen, until at 4 p. m. they were practically the same as shortly after the operation, just twenty-four hours previously. A blood count on the day after the operation showed that the red blood cells had fallen to 2,850,000, the hæmoglobin to 45%, while the white blood cells remained about the same. Before abortion the temperature tended to reach 104°, but varied after ice sponges between 102° and 103°. Two days after abortion the temperature began to fall gradually until it touched normal on Nov. 30th, the 22nd day.

On Dec. 8th, the 30th day, the patient had a severe chill and the temperature rose to 103.6°. This was followed by two other chills on the 9th and 10th, which probably marked the onset of a

slight pleurisy and pneumonia which interrupted the convalescence. The patient was discharged on Jan. 19th, (72nd day), her temperature having been normal for sixteen days.

The following report was made by Dr. Cole:

Nov. 19th, eleventh day. Widal with mother's blood, positive in one hour, dilution of 1 to 50.

Nov. 20th. Typhoid bacilli cultivated from the urine.

Nov. 17th. Blood culture. Seven plates. Negative for typhoid bacilli.

Nov. 23rd. Blood culture. Sterile.

Dec. 1st. Blood culture. Sterile.

The fœtus was completely enclosed above the knees by membranes. It was not in the least macerated and presented no unusual features. It measured 15 cm. in length and weighed 100 grams. With aseptic precautions, the fœtus was opened and material obtained for bacteriological examination, a Widal and a blood count. As it was thought that the organisms if present at all would not be numerous, the entire heart, large bits of the liver, and about one cu. cm. of blood were used for inoculating the media. Large quantities of bouillon were used as media to so dilute the blood that it would not exert much agglutinative action over the organisms and thus inhibit their growth. After eighteen hours in the thermostat, the cultures showed signs of growth. Agar plates were then made and the colonies thus obtained were transplanted to various media. The organism was a bacillus which fulfilled all of the morphological and cultural requirements of the typhoid bacillus, and was agglutinated in seven minutes by serum from a known typhoid case in dilution of 1 to 50.

The Widal test with serum from the fœtal blood was negative, both in dilutions of 1 to 10, and 1 to 50, no agglutination being noted in one hour. The test was made by Dr. Cole. Dr. Emerson found the fœtal blood count to be:

Red blood cells	1,168,000
White blood cells	9,000
Hæmoglobin	25%

The nucleated red blood cells were all normoblasts and intermediate forms, no typical megaloblasts being seen.

The autopsy of the fœtus was negative. The organs appeared

normal, and there were no intestinal changes. Microscopical examination of sections from the fœtal spleen, liver, lungs and kidneys was negative from a bacteriological point of view.

The placenta immediately after removal was placed in a sterile vessel and examined shortly after. Cultures were made in the same manner as with the fœtus, but the typhoid bacillus could not be obtained, the colon bacillus alone being grown. It appears likely, however, that the colon bacillus was a contamination, obtained doubtless during the manual removal of the placenta. Macroscopically the placenta was normal. Its dimensions were 10 x 8 x 1 cm., and its weight 110 grams. Teased villi appeared normal. There were no large infarcts. Microscopical examination of sections of the placenta showed numerous hæmorrhagic infarcts, also an early decidual endometritis. The latter probably developed during the twelve hours the placenta remained in the uterus, after the expulsion of the fœtus. Examination of sections stained to show typhoid bacilli was negative.

Immediately after the removal of the placenta a uterine culture was obtained. The tube filled with blood and consequently amounted to a maternal blood culture. The smears were negative for organisms. Bouillon tubes and agar plates were inoculated with the contents of the culture tube, but remained sterile for six days in the thermostat at 37°. One week after the abortion, a second culture was taken from the uterus. The lochia thus obtained presented no unusual features. When the cervix was first exposed a small amount of thin yellowish pus was seen about it. Slips taken from the lochia showed two types of bacilli. The first was a small, slightly lanceolate shaped organism about twice as long as broad and arranged in pairs. It retained Gram's stain and could not be grown in aerobic cultures. The second bacillus was larger, two or three times as long as broad, decolorized with Gram's stain and fulfilled the various cultural tests of typhoid bacilli. It also was agglutinated with serum from a known typhoid case in dilution of 1 to 50. It is a matter of some interest that the agar plates inoculated directly with lochia in the usual manner remained sterile. The organism was obtained by inoculating an Erlenmayer flask containing about 75 cm. of bouillon with about one cu. cm. of the lochia, and obtaining agar plates eighteen hours later.

Case II.—M. M. White. Age 32 years. Admitted October 15, 1900, on the fifteenth day of typhoid fever, complaining of pain in the bones and headache.

Family History.—Negative.

March 20th. Since the patient's admission two of her children have been taken with typhoid fever.

Past History.—Patient has always been well and strong. She has had seven children, all born spontaneously. The oldest child is 13 years, the youngest two years. She has had two abortions. Menstruation began at 13 years, and has always been regular.

Present Pregnancy.—Menstruation ceased on Feb. 2nd. Fœtal movements were first felt at the end of July. Up to the onset of present illness, the pregnancy has been uneventful.

Present Illness.—There has been a small epidemic of typhoid in the patient's neighborhood. Two weeks before admission she complained of malaise and diffuse general pains. She had some diarrhœa, severe headaches and thinks she had fever. Her symptoms steadily became worse and one week after their onset, she took to bed. At that time she had definite fever, also a painful dry cough.

Examination on Admission.—She is a small-framed, rather emaciated woman who looks sick. The tongue is coated and the teeth badly decayed. There is no respiratory distress. She has a fairly marked goiter. The lungs are negative, save for a few râles in the bases. Over the heart there is a soft systolic murmur best heard in the pulmonic area. The pulse is 120, regular in force and rhythm. It is rather empty, and suggestive of dicrotism. The liver dulness extends in the mid-sternal line, from the fifth rib to just above the costal margin. There is some abdominal tympany. The spleen is not palpable. There are several rose-spots scattered over the abdomen and the back. The uterus is enlarged to the size of a seven and half month's pregnancy and is contracted so firmly that the fœtus cannot be outlined. The fœtal heart beat is 180, and is heard in the lower right abdominal quadrant. (The mother's temperature is 102°.) The pelvis measures: spines, 25 cm., crests, 27.5 cm., trochanters, 29.5 cm., Baudelocques dia., 18.5 cm., diagonal conjugata, 12 cm., estimated conjugata vera, 10 cm.

There are some well-marked varicose veins over the left calf and foot.

Up to the time of delivery, the course of the disease was fairly uneventful. The fever was characterized by intermissions. It seemed to present also three general curves. The first fell gradually from 102.5° on admission on the 15th day to 99.5° on the 22nd day, the second fell from 103.5° on the 23rd day to 99° on the 34th day, and the third fell from 103° on the 36th day to normal on the 44th day, four days after delivery. The fœtal heart was profoundly influenced by the maternal temperature, varying from 150 at 99°, to 180-200 at 102.5° or 103°. When the temperature rose to 103° or over, the fœtal heart always became so rapid that it could not be counted. The child lay in L. O. I. A. The uterine contractions were also influenced by the fever, and during the rise, they occurred at more frequent intervals, and between the contractions the uterus remained more firm than in the afebrile periods. Careful search of several blood slides showed neither malarial organisms nor pigmented white blood corpuscles. The leucocytes varied from 6000 on admission to 18,000, on the 36th day, but generally were below 12,000. There were no symptoms noted to account for the leucocytosis. The Widal reaction was extremely suggestive on the 17th day, and on the 27th day it was positive in dilution of one to fifty.

On October 26th, the fortieth day, the patient insisted that she was having "labor-pains," although the contractions did not appear to be longer or firmer than those frequently noted during observation. Near midnight the contractions had increased in frequency, coming on at intervals of eight minutes. Shortly after, the cervix was found to be completely obliterated and dilated, and the head presenting at the level of the ischiac spines in L. O. I. A. As the pains were not excessively severe the labor was allowed to progress, and after a second stage of two hours the child was born spontaneously after remarkably few expulsive pains.

The mother stood the labor very well, had but very moderate bleeding, and was discharged in convalescence, twenty-nine days after delivery, and sixty-nine after the onset of the disease.

The child was a male, 2450 grams in weight, 45 cm. in length, and was apparently premature at the 36th week. It possessed

remarkably little vitality, but was kept alive for seventy-one days in the incubator. It was artificially fed. During the first few days of life there was inanition fever. Immediately after birth, many small reddish-pink maculæ, about pin-head size, were noted about the upper abdomen, chest and shoulders. These disappeared on pressure and suggested rose-spots. There were also several larger erythematous maculæ, scattered over the chest, upper abdomen, shoulders and legs. They were purplish-red in color, 5 or 6 mm. in diameter, and had smaller whitish central papules. When seen by Dr. Osler, nine hours after birth, only the larger maculæ were present, and these disappeared within the next twenty-four hours. The Widal, nine hours after birth, was negative in one to ten dilution. At that time the Widal with the mother's blood was positive in one to 50 dilution, and negative with the colostrum in one to 10. The Widal, with the child's blood, was also negative on the 36th day, and on the 72nd day, immediately after death. As the mother had returned to the country, permission to make an autopsy could not be obtained until 42 hours after the child's death. The result was negative. Bacilli coli communis were cultivated from the heart's blood and fœtal organs.

The placenta was received into a sterile basin and cultures were immediately made. Blood cultures from the cord and fœtal vessels were taken, and flasks containing large quantities of bouillon were inoculated with large bits of placental tissue. In all, fifteen primary cultures were inoculated which appeared unchanged 36 hours later. Through an accident to the thermostat on the following night the cultures were destroyed, but slips taken from the flasks shortly after were negative for organisms. The placenta was normal macroscopically and microscopically. It measured 14 x 12 x 2 cm., and weighed 245 grams. A few very small white infarcts were noted, but there were no hæmorrhagic infarcts noted upon macroscopical and microscopical examination. There were no bacilli seen while examining many sections stained to demonstrate the typhoid bacillus.

Case III.—The following is reported only for the observation as to the Widal reaction: M. B. White. Age 26 years. Admitted June 28th, discharged Aug. 13, 1897.

The patient was admitted on the twenty-second day of typhoid fever. On the 48th day, after 12 days of normal temperature, there was return of fever. On the third day of the relapse, she gave birth to a still-born sixth month fœtus. Neither the placenta nor fœtus were examined bacteriologically. The blood of the placenta gave a rather slow positive Widal, but the blood of the child caused no agglutination.

The history of the study of typhoid fever during pregnancy may be said to begin with the observations of Louis in 1829. Chomel in 1834, called attention to the rarity of the disease during the puerperium but made no mention of its occurrence during pregnancy, nor did Velpeau a year later, in his work on obstetrics. Forget in 1841, in his Traité de l'Entérite folliculeuse, reports several observations during pregnancy. Cazeaux, in 1844, is the first to discuss the subject in an obstetrical text-book. William Cummins, in 1859, reports several cases in the *Dublin Quarterly Journal.* Since then it has been studied by hosts of observers, especially in France and Germany, and has formed the title of many French theses. With the advent of bacteriology it has been of great interest in connection with the question of placental transmission.

There are not many accurate statistics as to the frequency of this complication of pregnancy. Liebermeister in 1420 typhoid cases found but 18 associated with pregnancy, and Zuelzer in a series of 1852 cases in Vienna, noted but 24. This gives percentages of 1.2% and 1.3%, but these figures make no distinction between men, women, and children. Curschmann in 1817 cases of typhoid in female patients of Leipzig and Hamburg, found 45 associated with pregnancy (2.5%), Goltdammer noted 26 in 640 (4%), and Martinet records 16 in 460 (3.5%). In this hospital (Johns Hopkins), the association of pregnancy has been noted but 4 times in 289 cases of typhoid in the female (1.4%). Thus, for a total of 3206 female patients, pregnancy and typhoid existed in 91 instances, less than 3%, but these statistics include typhoid in the young and aged as well as in the child-bearing period.

The observations of various authors show that contrary to the older view, pregnancy affords no protection against typhoid fever. In epidemics in small towns, where pregnant women are exposed to the contagion, they contract the disease in about the same

proportion as non-pregnant women. Müller states that complications of typhoid are rare in pregnancy, and that if there is no interruption of pregnancy, the reaction of typhoid is apt to be slight. If the pregnancy is interrupted in the early weeks of the disease, the patient is apt to be but little affected by the miscarriage; later in the disease, however, when she is weakened and emaciated the reaction is apt to be more severe. Complications of labor, as hæmorrhage, are not more apt to occur than in normal cases. The maternal mortality is given by Müller as 21%, which is considerably higher than that of Sacquin's tabulations, 16%, being 37 deaths in 233 cases. Curschmann, on the other hand noted death but in 7.8% of the 38 cases in the Hamburg epidemic. In the Johns Hopkins Hospital, the pregnancy was interrupted in three of the four cases, and the fourth patient died without miscarrying.

As to the frequency of abortion, we obtain the following from Sacquin, whose statistics include those of most of the authors usually quoted: Total number of collected cases 310. Interruption of pregnancy in 199. This series is further subdivided, according to the completeness of the data. Thus in 233 cases, abortion, miscarriage or premature labor occurred in 150, with a maternal mortality of 16% (37 cases). In 169 cases where the data were given more in detail, it was found that the pregnancy was interrupted in 103 instances, with 22 maternal deaths (13%). 124 of these cases were less than seven months pregnant, and 45 were beyond that period. 72 cases of the first group, either aborted or miscarried. The remaining 52 were not thus affected. Maternal death occurred in 16 cases (13%).

In the 45 cases of the second group (over seven months pregnant) premature labor followed in 31. There were 6 maternal deaths in this group (13%).

Sacquin tabulated 59 cases that did not come to term, to show the relation of abortion to the period of pregnancy, and found:

2nd month of pregnancy,	2	cases	aborted.	
3rd " "	22	"	"	
4th " "	11	"	miscarried.	
5th " "	10	"	"	
6th " "	1	"	"	
7th " "	8	"	premature labor.	
8th " "	4	"	"	"
9th " "	1	"	"	"

To show the relation of abortion to the duration of the fever, he tabulated 51 cases in which the pregnancy had been interrupted.

	Before the 7th month of pregnancy.	After the 7th month of pregnancy.
1st febrile week	3 cases	6 cases
2nd " "	11 "	13 "
3rd " "	5 "	3 "
4th " "	1 "	2 "
During convalescence	5 "	1 "
" relapse	1 "	

Thus it may be concluded that typhoid fever is more commonly seen in the first half of pregnancy, consequently abortion and miscarriage occur more frequently than premature labor; and that pregnancy is most apt to be interrupted in the 3rd month and in the second week of fever.

Various causes have been advanced to account for the frequency of abortion, but apparently the mechanism is more complex than is usually believed, and no one theory, thus far, seems to hold good for all cases. The experiments of Claude Bernard, and of Max Runge furnished the basis for the view, that the high and prolonged elevation of temperature acted directly upon the fœtus, causing its death, and upon the uterus exciting its contractions, and consequent abortion. Winckel showed that the fœtal heart rate increased in direct proportion to the maternal temperature, as did Georgi in Gusserow's clinic, and Gusserow stated that the danger to the child is proportional to the elevation of the temperature, and to the duration of this influence. There are, however, cases in which the pregnancy has not been interrupted in spite of a temperature of 104° maintained for five to nine days, and without fœtal death. Cases are also known to pass through the original attack and recurrence as well, to give birth to premature but live children during convalescence. Doléris, Doré, Sacquin and others contend that this influence is not of greatest importance, and Doléris and Doré by obtaining conditions which they believed more closely approached the state of an individual during fever were able to subject animals to very high temperatures without causing abortion or death of the fœtus.

Goltdammer advocated the view that hæmorrhagic endometritis was the cause of abortion. This theory, however, has received

but little support, and the majority of observers believe that if typhoid endometritis ever occurs, it is very rare. Some, as Grisolle, have thought that in cases with pulmonary complications, the shock of coughing may precipitate the abortion, while others, as Bourgeouis, believe that the uterine contractions may be reflexly excited by the spasmodic intestinal contractions. Fœtal septicæmia and consequent fœtal death may cause abortion, but in many cases the child is live-born and consequently "fœtal typhoid" cannot be proven unless death intervenes, giving opportunity for bacteriological study. Sacquin believed that in cases in which the pregnancy was interrupted without fœtal death, the process was a very complex one, and was probably due to a toxic action affecting the medullary centers, and causing an excessive reaction of the pregnant uterus. This view is most probable and should explain the greater number of cases.

In the earlier cases, proof of the transmission of typhoid fever from the mother to the child was naturally sought in lesions of the intestine, similar to those in the adult. Although cases have been adduced by Charcellay in 1840, by Manzini in 1841, and later by Weiss, and others, it is probable from the study in recent years, that these early cases were not fœtal typhoid, as the transmission of the disease can only be ascertained by bacteriological methods. Before considering cases in which study has been made of the fœtus, and the transmission of the typhoid bacillus proven, we will review the course of pregnancy in other acute diseases, and the question of the placental transmission of the various diseases.

The majority of the earlier cases adduced as placental transmission were those of exanthemata, in which the clinical findings of the disease in the newly-born corresponded to those of the mother. There are many objections to receiving the majority of these cases as proven, for diseases possessing a bacteriological ætiology, as a rule cause no macroscopic lesions in the fœtus. The diagnosis of the diseases of the newly-born also presents many difficulties, and where the lesions do not appear until after birth it is impossible to say with certainty whether the disease was acquired in utero, contracted while passing through the birth canal, or postpartum.

The better acquaintance with diseases that manifest themselves in the fœtus in utero, or shortly after birth, has led to the recognition of two possibilities of hereditary transmission. These are:

I. Germinal: where the infection is directly associated with the germinal cells, and occurs at the time of conception, and

II. Placental: where the organisms causing the disease are transmitted from the mother to the fœtus, by means of the placental circulation.

Germinal infection is positively proven in syphilis and perhaps in tuberculosis.[61] This form of infection will not be considered in this paper. Placental transmission, although recognized in many diseases, is by no means the rule, and it is to be noted that where bacteria are proven to have passed through the placenta, the resulting disease is as a rule a fœtal septicæmia.

For many years it has been well known that variola may be transmitted to the child in utero, yet these cases are rare in comparison with those in which the fœtus has shown no trace of the disease. Curschmann stated that it was a most infrequent occurrence, and Eimer and Welch both emphasize its rarity. A well known positive case is that of Mauriceau, the celebrated French obstetrician, who was born with pock marks. Congenital smallpox, however, is almost uniformly fatal (Tarnier and Budin). Charcot states that the mother may have varioloid, and yet the child be born with the marks of smallpox. Chaigneaux reports the case of a woman employed as a chambermaid to one afflicted with variola, who gave birth to a premature still-born child marked with the pustules of the disease. The woman herself apparently did not have variola. One or both twins may show the lesions (Chantreuil, Madge), and Jobard claims that the fœtus may be marked as early as the third month.

Smallpox is a most unfavorable complication of pregnancy, and abortion and maternal death frequently occur. The hæmorrhagic form is most fatal, all of Meyer's thirteen cases resulting in death. In this class of cases the mother frequently dies before aborting.

Van der Willigen observed that smallpox was more fatal in the pregnant woman, his statistics being drawn from the study of 80 cases of pregnancy, occurring in the 1143 cases of smallpox in the Rotterdam epidemic of 1895. He found the mortality for the non-pregnant women to be 11%, and for the pregnant 15%. The mortality was also higher in multipara than in primipara,

being 17% as opposed to 9%. During the last half of pregnancy the mortality was 20.8%, while in the first half it was 6¼%. The fœtal mortality in this series was 45%, and in no case was intrauterine variola noted. Vinay also noted the increased maternal mortality during pregnancy. He reports a mortality of 36% in 235 cases, as compared with 25% for the non-pregnant women.

Voigt gives the following tables for 182 collected cases:

L. Meyer,	76 cases.	Interruption of pregnancy in	31,	maternal death in	22
Knecht,	46	"	"	"	27,	"	"	16
Legroux,	8	"	"	"	5,	"	"	4
Rivet,	11	"	"	"	7,	"	"	9
Jobard,	41	"	"	"	20,	"	"	10

Reports by Barthélemy, Kahler, and Sangregorio add 115 cases, in which the pregnancy was interrupted 52 times, with maternal death in 43 instances. Franque reported 48 cases. Thirty-two of these either aborted or miscarried, and in no instance was there trace of smallpox in the fœtus. In two of Meyer's cases, however, a sparse eruption of smallpox was noted in the fœtus. As will be seen by reference to the literature quoted, the majority of these observations were made several years ago, and now that vaccination is so universal it may be expected that the mortality and morbidity in pregnancy will be consequently reduced, and congenital smallpox be even more of a rarity.

It was formerly held that smallpox in the mother conferred immunity upon the unborn child (Chambrelent), but the more recent observations do not confirm this theory and the evidence indicates that the disease is apt to ensue with fatal result, unless the child be vaccinated at birth.

This view is strengthened by the observations as to the possibility of intrauterine vaccination. The weight of authority is that such vaccination is not possible, and save for a slight transient passive immunity, there is no protection to the child caused by the successful vaccination of the pregnant mother. This is contrary to the older teachings of Bollinger, Burckhardt and others, and is based upon the careful experiments of Gast, Behm, Wolff, and Palm. Gast successfully vaccinated the women during the last months of their pregnancy. In none of the 16 children was vaccination unsuccessful immediately after birth. Behm successfully vaccinated 29 women during their pregnancy. The children of

25 of these women reacted to the vaccine shortly after birth. Of the remaining 4, 3 failures were found to be due to inactive lymph; the fourth case could not be explained in this manner, and Behm thought that there may have been intrauterine vaccination. Wolff vaccinated twenty pregnant women, seventeen of these reacted. The children of these seventeen women all reacted typically to the vaccine after birth. Palm vaccinated fifteen newly-born children whose mothers had been vaccinated during pregnancy. Only two of these children did not react, and in both of these cases the vaccination of the mother during pregnancy had also been unsuccessful.

There are comparatively few observations concerning the intrauterine exanthemata that are not open to doubt, and until the materies morbi of these various diseases is fully known, the question of its possibility will be open to discussion. Ahlfeld, and many other careful observers, claim that there are no positive cases of placental transmission in scarlet fever, although Speier found several cases in which the child is said to have shown a scarlet eruption. Leale has reported a case which he believes is undoubted, and has collected a number of others from the literature, as did Ballantyne and Milligan. The literature concerning these cases, as would be expected, is naturally very much confused with that of measles.

Placental transmission of scarlet fever cannot be proven by clinical cases, as there are undoubted cases in children and adults in which the period of incubation was less than twenty-four hours (Thomas), consequently unless we are able to prove the presence of the materies morbi in the blood of the mother and the child at birth, it seems more probable that the infection occurred during the passage of the birth canal. The same statement may be made concerning measles and erysipelas, although Clarus, years ago, recorded a case in which the child delivered by a post-mortem cæsarean section was covered with a characteristic measles rash. Thomas mentions six cases collected from literature as congenital measles, and Lomer, and Fiori also record others. There are also cases in which women sick with erysipelas have given birth to children with lamellar scaling (Stratz, Kaltenbach, Runge).

Lebedeff records the case of a seven months' fœtus which presented alternate patches of red and white upon its skin. After

death streptococci were cultivated from the subcutaneous fat, these however could not be demonstrated in the placenta or cord.

Tarnier called attention to the fact that desquamation in the healthy new-born infant is not an infrequent occurrence, which observation has frequently been confirmed by the author.

Scarlet fever is but rarely noted in pregnancy and frequently results in abortion. Olshausen collected but seven cases of scarlet fever in pregnancy, as compared with 134 in the puerperium. The seven cases were those of Dance, Koch, Hervieux, Cremen, Hardy and two of Braxton Hicks. Five of these cases aborted and three died. It is possible that in many of the cases noted in the puerperium, the rash was one frequently noted in association with puerperal infection, rather than true scarlet fever. Measles is also infrequently noted in pregnancy. Like scarlet fever, it is apt to cause abortion and maternal death (Tarnier).

Asiatic cholera is a most dangerous complication of pregnancy, and observers agree that the mortality is higher in the pregnant women. Abortion is very common although maternal death may ensue before expulsion of the fœtus. Schütz states that the mortality in the recent Hamburg epidemic was 57%, and interruption of pregnancy by abortion or premature labor 54%. According to Ahlfeld there were no cases of placental transmission noted. Baginsky observed 23 cases of cholera during pregnancy. Maternal death occurred in 14 cases, and abortion or premature labor in 10. Queirel reported 67 cases of cholera during pregnancy. Maternal death occurred in 39, and abortion or premature labor in 29 cases. Cholera is but rarely transmitted to the fœtus. Tizzoni and Cattani report the only positive case. The bacillus was cultivated from a five months' fœtus aborted on the fifth day of the attack. Lustig obtained negative results in seven cases, as did Vitanza in five, although in this last series, the organism could not be cultivated from the maternal blood.

Over a third of the women suffering from cholera during pregnancy have uterine hæmorrhages, and Slavianski found a hæmorrhagic endometritis to account for the abortions, although the toxæmia and the dehydration of the mother's blood, together with the sinking blood pressure may be of major importance.

There are several positive cases of placental transmission in tuberculosis, but with more modern methods of research this list

is growing. Birch-Hirschfeld, Merkel, Demme, Sarwey, and Baumgarten have reported cases in which the tubercle bacillus, or caseous material has been found in the newly-born fœtus, and Hauser has collected 18 cases from the literature in which the transmission was demonstrated. From a review of the literature, Lubarsch concludes that placental transmission is not uncommon in this disease, and that it may occur not only in acute miliary tuberculosis, but in the chronic ulcerative forms as well, especially if there be slight dissemination.

In spite of the rarity of anthrax, there are several cases in which placental transmission has been proven. Speier was able to find but the one case of Paltauf, in which the bacillus was cultivated from the lung of a five months' fœtus. Ahlfeld mentions a case reported from the Leipzig Frauenklinik, and Rostowzen reports three cases in which the bacillus was cultivated from the tissues of the child. All of the above cases resulted fatally.

It has not yet been demonstrated that influenza can be transmitted to the fœtus. In the milder epidemics the disease probably exerts but little effect upon the course of pregnancy, although the severer forms may prove a most dangerous complication. Felkin reports premature labor in six out of seven cases, Hintze reports an epidemic of eight cases in the Leipzig Frauenklinik, with maternal death in three. Müller reported 21 cases with abortion or premature labor in 16. Amann records six cases with interruption of pregnancy by abortion or premature labor.

The transmission of the pneumococcus from the mother to the fœtus is, according to Lubarsch, fairly frequent. Marchand was one of the first to report the transfer of lobar pneumonia to the fœtus, but in his case there was no bacteriological proof. Levy, Netter, Viti, Carbonelli, and Birch-Hirschfeld have all adduced bacteriological proof that the bacteria found in fœtal blood, were identical with those in the mother's. Furthermore, Levy and Netter have shown that where the coccus has been transferred to the fœtus, and the lung has not functioned, a pneumococcus septicæmia results, but that, if the lungs function after birth, pneumonia may develop.

Pneumonia is an exceedingly dangerous complication of pregnancy, as abortion is very apt to occur, and to result fatally.

It has been claimed that malaria may be transmitted to the

fœtus, and pathological changes as splenic tumor have been described in children born during this disease, yet in spite of the fact that the plasmodium is so well known, and may be present in the maternal blood in greatest numbers, there are no authentic cases in which the organism has been demonstrated in the fœtus at birth. The disease has been frequently associated with pregnancy in the Johns Hopkins Hospital. As a rule the children are born at term, and in four cases of which I have notes, it has been impossible to demonstrate the organism from the blood vessels of the placenta, cord, or fœtus, although in each instance such demonstration has been made with the mother's blood before and after labor. It would appear likely, however, that the pernicious type of this disease would prove a grave accident in pregnancy. Goth reports 19 out of 46 cases ending in premature labor, and Edmonds states that this is frequently noted in Africa.

We have seen from the above review, that acute diseases are apt to prove more dangerous to the pregnant woman; and, that placental transmission, proven *possible* in the majority of diseases, is by no means a constant feature.

There are a considerable number of recorded investigations concerning placental transmission of typhoid in man, but the number of positive cases is not large, especially if we class as doubtful the earlier cases, and those in which no attempt has been made to exclude the members of the colon group of bacilli. Experimentally the typhoid bacillus has been proven to pass from mother to fœtus in rabbits and guinea-pigs.

E. Fraenkel subcutaneously inoculated a pregnant guinea-pig with the typhoid bacillus. The organism was recovered from the fœtus and the placenta was found to be studded with "hæmorrhages."

Chantemesse and Widal inoculated (peritoneal) a pregnant guinea-pig with the typhoid bacillus. Abortion followed in twenty-four hours, and the organism was recovered from the fœtal spleen and liver. In another case the typhoid bacillus was found in the amniotic fluid, twenty-four hours after inoculation of the mother.

Frascani inoculated pregnant rabbits with cultures obtained from a fœtus aborted during typhoid. In his twelve experiments,

abortion occurred nearly constantly, and as a rule the bacillus was transmitted to the fœtus. Lesions of a hæmorrhagic type were found in the placenta of such cases.

The first case reporting the cultivation of typhoid bacilli from the fœtus of man is recorded by Reher. The six months' fœtus was still-born on the nineteenth day of typhoid. The autopsy was negative. From the liver of the fœtus colonies developed which are described as typhoid colonies. The early date of this report (Oct. 19, 1884) makes the case doubtful, inasmuch as the colon bacillus, which was described in the same year, was not well known.

Neuhauss reports a case in 1886. Abortion occurred during convalescence, and after a relapse. The typhoid bacilli are stated to have been obtained from the lungs, spleen, and kidneys of the four months' fœtus. This case must also be considered doubtful.

Eberth's case in 1889 admits of less doubt. The six months' fœtus was still-born during the third week of the fever. The typhoid organism was recovered from the fœtal heart, lung and spleen. Gelatine, agar and potato were used as culture media. At this time the growth of the organism upon potato was thought to be diagnostic. Bacilli were found in the intervillous spaces of the placenta, otherwise the placental examination was negative.

Hildebrandt, in the same year, reports the cultivation of the typhoid bacillus from a child born prematurely at eight and one-half months on the fifteenth febrile day. The organism was obtained from the blood of the umbilical cord, the heart, spleen, liver and mesenteric gland, and was grown upon all of the media now in general use, save glucose agar.

In the case recorded by Ernst in 1890, the child was born four weeks before term on the tenth day of fever. For three days it did well, but then developed icterus, and a specky exanthema and died after ninety-three hours of life. Cultures from the heart's blood and spleen developed bacilli described as typhoid. Bacilli were found in sections of the muscles, heart, blood-vessels of the femur, brain, and Malpighian tufts of the spleen. The observer believed that a fall shortly before the onset of fever was of importance in preparing the placenta for bacteriological transmission. The placenta, however, does not appear to have been examined.

Balp, in 1891, reports a mixed infection, the organisms being

the typhoid bacillus, and the yellow pus coccus. These were recovered from the liver and spleen of a six months' fœtus, born to a woman of 52 years, while in the fifth week of typhoid. The child lived four hours, and the mother but four days.

Frascani, in 1892, appears to have differentiated the organism obtained from the colon bacillus. He cultivated the typhoid bacillus from the liver of an eight months' macerated fœtus, born during typhoid five weeks after admission to the hospital. Cultures taken with a hypodermic syringe from the spleen of the mother developed the same germ, while cultures from the uterine lochia remained sterile. The placenta showed numerous hæmorrhagic infarcts.

In Janiszewski's case in 1893, the eight and a half months' fœtus lived five days. It was born on the 20th day of typhoid. Cultures were taken from the fœtal lung, spleen, kidneys, mesenteric glands, and from the intestine near the ileocæcal valve. These developed colonies which from growth on agar, gelatin, bouillon and potato are stated to be typhoid. There is no note as to the placenta.

Freund and Levy's case is perfectly convincing. The fœtus measured 20 cm. in length, and was aborted during the fourth week of the fever. Typhoid bacilli were cultivated from the heart and spleen. The placenta was normal on macroscopic and microscopic examination.

Dürk's case is likewise authentic, and proved to be a mixed infection. The child was born shortly before term and lived for nine hours. Birth occurred in the fourth week of the fever. The typhoid bacillus, and the staphylococcus pyogenes albus were obtained from the liver and spleen.

Etienne, in 1896, records the transmission of the typhoid bacillus to a four months' fœtus, aborted on the twenty-ninth febrile day. The placenta was normal on macroscopic examination.

Speier, in 1897, appears to be the first to verify the organism obtained from the fœtus by the Widal agglutination test. Abortion in this case occurred on the twenty-first day of fever, and in the fourth month of pregnancy. His report is very complete. The placenta was permeated with microscopical hæmorrhagic infarcts.

Fordyce, in 1898, records a case in which the typhoid bacillus

(probably) was isolated from the fœtus. The report is not clear. Apparently the organism was not tested by the Widal, in order to absolutely prove its identity. Serum from the peritoneal cavity of the five months' fœtus agglutinated known typhoid organisms. The dilution in which the reaction was obtained is not given. Save that no bacilli were seen in sections, there is no note as to the condition of the placenta.

Horton-Smith, 1900, refers to a case of Dr. Andrews, in which abortion occurred during typhoid in the fourth month of pregnancy. Typhoid bacilli were cultivated from the fœtal heart and spleen, and their identity was established both by the cultural growth and by the Widal test.

Richardson, in 1900, reports two cases. In Case I, the bacillus was recovered from the fœtal liver.

In Case II, the organism was isolated from the heart, liver and kidney of the four months' fœtus. In both cases, the Widal test was used to confirm the diagnosis of the typhoid bacillus.

Blumer's case differs considerably from any of those recorded above. A child, nine days after forceps delivery, died of an illness which developed on the third day, and which was characterized by hæmorrhages from the uterus, bleeding from the gums, petechiæ and convulsions. Typhoid bacilli were recovered from the umbilical cord, lung, bile and spleen. Cultures from the heart, liver and kidney remained sterile. The mother at time of delivery was healthy. It was ascertained that when five months' pregnent, she was confined to her bed for three weeks, with an illness that was marked by intermittent fever, occasional chills and constipation. This illness was judged to be typhoid, on account of the absence of malaria in the patient's neighborhood. The Widal test was not tried either with the maternal or fœtal blood. This is the first recorded case in which the child was not born either during the attack of typhoid or shortly after. It has seemed better, on account of the history, to class the case as a congenital infection, rather than infantile typhoid, as it appears unlikely that the organism gained access to the fœtal circulation after delivery, through lesion of the umbilical cord. This assumes that the bacilli remained latent in the mother or child until after delivery.

Bolton, in 1901, reports a case in which the typhoid bacillus was cultivated from the gall-bladder and spleen of a five months'

fœtus, extruded on the twenty-fifth day of typhoid. The organism thus obtained was agglutinated with blood serum from a known typhoid case, and also with the blood of the fœtus. The mother's blood gave a Widal reaction in one to forty dilution, and the fœtal blood in one to twenty.

That the typhoid bacillus is not always transmitted through the placenta, may be seen from the cases recorded by various observers, in which cultures taken from the fœtus of a typhoid mother remained sterile, or at least did not contain the typhoid organism. Among the cases thus reported are those of E. Fraenkel and Simmonds, E. Fraenkel and Kiderlen, E. Fraenkel (2 cases), Frascani (2 cases), Legry, Flexner, Charrier and Apert, Etienne, Darling, and Bolton (2 cases). Giglio's case must also be added to this list, for the organism obtained has no points of resemblance to that of typhoid fever. The cases of Chantemesse and Widal, and Legry, which have been incorrectly quoted by some authors as positive cases of placental transmission, cannot be considered at all, for study of the original reports shows that the bacteriological examination did not extend to the fœtus.

The above indicates that organisms do not pass from the mother to the fœtus with any degree of regularity. It also shows that some bacteria are more apt to be transmitted than others. Many observers have turned their attention to the factors involved in such transmission, but as yet there is not perfect agreement as to the determining factor.

Max Wolff, from numerous experiments upon pregnant animals inoculated with anthrax bacilli and various other pathogenic organisms, came to the conclusion that placental transmission is possible only where there are hæmorrhagic infarcts or other gross lesions.

The experiments of Malvoz confirm those of Wolff. He inoculated pregnant rabbits with the bacillus of chicken cholera, and was able to demonstrate placental transmission and the presence of hæmorrhagic infarcts in nearly every case. The placentæ of rabbits inoculated with anthrax bacilli showed no gross lesions, and he could prove placental transmission only in four of 163 experiments. By inoculating guinea-pigs, however, with anthrax he found numerous hæmorrhagic infarcts in the placentæ, and proved placental transmission in over 50% of cases.

Birch-Hirschfeld, from numerous observations, concluded that transmission of bacteria may occur without gross lesions of the placenta: that single bacilli may penetrate the chorionic villi, and in cases where the bacilli are very numerous in the blood-vessels, as in anthrax, that they may penetrate the "anchoring villi" and thus reach the fœtal placenta without passing through the intervillous spaces.

Virchow, in a discussion of this theory, stated that the pathological lesions in the placenta may be slight, and that circulatory disturbances, as stasis and thrombosis may be important factors in the process.

Lubarsch noted anthrax bacilli in a hæmorrhagic area of a rabbit's placenta where transmission was proven by fœtal cultures. Bacilli were also demonstrated in chorionic villi in which the epithelium had been altered by the hæmorrhage.

Speier, in his typhoid case, did not find bacilli in slides that showed hæmorrhagic infarcts, although bacilli were found in apparently normal villi.

Experiments and clinical observations of many investigators show that placental lesions of the hæmorrhagic type are more frequently noted when the pregnancy has been complicated by some infectious disease of the mother, and although placental transmission has not been constantly observed in these cases showing hæmorrhagic lesions, it would seem that they favor the transmission of the organisms causing disease. It is our opinion that the white infarcts which are found in 100% of all placentæ (Williams) are not portals of entry, except possibly in their very early stages. It is unfortunate that too much weight cannot be attached to the reports of cases of placental transmission in man, for in the majority of cases, no accurate description of the placenta is given.

Whether bacteria may pass through a normal placenta without causing lesions, is still a question that is open to discussion, and the demonstration of bacteria in the chorionic epithelium and tissue is needed for absolute proof. The majority of observers agree that some placental lesion is necessary, and taken separately, the virulence of the bacteria, their number, the time of their presence in the placenta, and their ability to remain there and multiply, are all items of importance.

Data concerning the Widal reaction in the fœtus of typhoid mothers is scarcely in form accurate enough to warrant definite conclusions. Although there are several cases in which the Widal has been obtained under such circumstances, there are many in which it has been absent. Authorities on the Widal are all emphasizing the necessity of high dilutions to prove its positive presence. In the Johns Hopkins Hospital, positive cases are restricted to those in which agglutination occurs with dilutions of one to 50 in one hour, and it is highly probable if this restriction could be applied in all cases thus reported, that a considerable number would be excluded. Such cannot be done, however, for as will be seen in the majority of cases, the mere statement as to its presence or absence is made.

The work of several observers tends to show that the Widal reaction cannot be obtained with the blood of normal children that have been born after a normal pregnancy.

Grünbaum tested the agglutinative power in the blood of five mothers and their newly-born children, in cases in which the mothers had never had typhoid. The serum was used once diluted. Only in a single case did the child's blood cause even a "weak" reaction. With the mother's blood, a "strong" reaction was noted in three cases, but the blood from the children of these mothers caused no agglutination, even in this dilution. He then tested the blood serum of two mothers who had had typhoid, one five and the other ten years previously, as well as the blood of their newly-born children. The mother's blood, once diluted, agglutinated typhoid bacilli, but the blood of the children caused no reaction.

Kasel and Mann studied the agglutinative power of the blood of mother and infant, in three cases in which the mother had had typhoid before pregnancy.

Case I. Mother had typhoid in August, 1897. On October 22, 1898, her blood caused agglutination in dilution of one to 50. On November 14th, when the child was two weeks old, its blood was negative in one to 50, also on December 27th, at which date the maternal blood caused agglutination in the dilution above given. On January 30, 1899, the maternal blood was positive in 1 to 25, while the child's blood was suggestive only in 1 to 1.

Case II. Mother had had typhoid 15 years before. When her child was three months old its blood was negative even in 1 to 1 dilution, although the maternal blood reacted in 1 to 50.

Case III. The mother had typhoid 21 years before the birth of the child. When the child was nine months old its blood twice caused no agglutination in 1 to 50, while the maternal blood gave a positive Widal, a few weeks later the Widal with the child's blood was only suggestive in dilution of 1 to 1.

Upon reviewing the literature we find a number of cases in which the Widal reaction has been obtained with fœtal blood. Based upon the presence of this reaction, many of these cases have been adduced as cases of placental transmission of typhoid, but such evidence alone is inconclusive and of no value, unless the actual presence of the typhoid bacilli has been proven, for it appears likely that under certain circumstances the agglutinins may filter through the placenta to the fœtus. Furthermore, from the evidence before us at present (see Remlinger's experiment below, and our Case I, page 285), it seems as if the agglutinins do not always form in the fœtal blood, in the presence of the typhoid bacilli, and we have been able to find but the one positive case of Bolton, and the somewhat doubtful case of Fordyce, in which both the Widal and the typhoid bacilli were found in the fœtal blood.

There is experimental evidence for the transfer of the agglutinating substances in animals, but the cases are not numerous.

Remlinger "immunized" a female rabbit with typhoid bacilli and bred her with a "non-immunized" male. The agglutinative power was kept at 1 to 400 during the period of gestation. The animal had four young. Only in three of these was the power of agglutination noted, one in 1 to 40 dilution and two in 1 to 30. The blood of the fourth animal caused no reaction. It shortly died and typhoid bacilli were recovered from the fœtal blood, the liver and spleen. He then bred an "immunized" guinea-pig to a "non-immunized" male. The agglutinating power of the maternal blood was kept at 1 to 200 during the period of gestation. Four of the young showed agglutinating power varying between 1 to 40 and 1 to 30.

The cases observed in man are as follows:

Chambrelent and Saint Philippe.—Birth of an eight months' fœtus during typhoid of the mother. The child was incubated and

artificially fed, but did poorly, having developed jaundice, an enlarged liver and bronchopneumonia. It was still alive however at the time of the report.

The Widal reaction was obtained from the mother's and child's blood, and from the serum of a blister upon the child's skin. None of the particulars concerning the reaction are given.

Mossé et Daunic.—The mother had passed through a mild attack of typhoid when six months pregnant. At term she gave birth to a normal, but small child. During her convalescence from typhoid her blood and colostrum both gave positive Widals. At time of birth the placental blood also caused agglutination of typhoid organisms. Twenty-four days after birth, both the maternal and child's blood was found to possess agglutinative power. On the 33rd day, the infant's blood caused the Widal reaction, although it reacted somewhat slower than either the maternal blood or milk. The tests used were macroscopic, one drop of serum to ten drops of a freshly inoculated typhoid culture in bouillon. The placenta was macroscopically and microscopically normal.

Griffith.—The blood of an infant, born during maternal typhoid, gave a positive reaction seven weeks after birth. The dilution is not given. The maternal blood was apparently not tested for the Widal.

Barber.—The child was born on the 3rd day of typhoid fever. The maternal blood reacted negatively in the Widal, thirty hours after delivery, but was positive on the 9th day of the fever. The infant's blood gave positive reaction on the 2nd, 7th, 14th, 23rd, 40th, and 70th days. Details of the Widal are not given.

Morse.—Birth on the 12th day of typhoid. The child was bottle fed. When two weeks old its blood caused a positive Widal agglutination. Dilution not given.

Wilson.[1]—Child born in third week of fever. Maternal death on the 2nd day of puerperium. Two weeks later, the infant's blood caused a positive Widal reaction.

Achard, reporting the case of Chaillous and Delamare.—The mother had typhoid during the sixth month. The child was born at term. The mother's and child's blood both reacted positively on the 3rd day. The dilution for the child's blood was one to two thousand. The colostrum also caused positive Widal.

[1] Quoted by Morse.

Mossé and Frenkel.—Five months' fœtus born during convalescence, fifty days after onset of typhoid fever. Fœtal autopsy negative. Apparently cultures were not made. Placenta normal, both macroscopically and microscopically. Maternal blood reacted positively in the Widal test as did the colostrum, and fœtal blood. The strength of reaction was one to one hundred for maternal blood, and one to ten for fœtal blood.

Etienne.—The patient died on the fifteenth day of typhoid before miscarrying. Autopsy of the five months' fœtus recovered from the uterus was negative. Fœtal cultures were sterile. The maternal blood gave a positive Widal, 1 to 150, the fœtal blood was positive 1 to 200, and the amniotic fluid also caused agglutination of typhoid organisms in 1 to 200 dilution.

Hare, reporting Krusen's case.—Delivery of an eight months' fœtus on the ninth day of typhoid. The infant's blood was found to react positively in the Widal in eleven minutes with dilution of 1 to 25, on the 27th day of life. There is no mention as to the Widal with the maternal blood.

Zängerle reports the case of a full-term child, born spontaneously during the third week of typhoid fever. On the 2nd day the child's blood reacted positively in dilution of about 1 to 60. Mother's blood positive in same dilution.

Kirton[1] reports the presence of the Widal reaction in both mother and newly-born child, birth occurring at term.

The case of Bolton given above (page 302) must also be added to this list.

There are also the following cases in which no transference of the Widal property was noted:

Shaw.—A patient passed through an attack of typhoid without miscarrying. Her child was born four months later. Tests with the maternal blood during the fever, and five and a half weeks after the birth of the child, gave a positive Widal reaction. The blood of the child however tested five and a half weeks after birth, and upon three other occasions caused either no agglutination or one slightly suggestive. The dilutions used are not recorded.

[1] Quoted by Bolton.

Cave.—A patient five months pregnant passed through an attack of typhoid without miscarrying. Ten months later the Widal was obtained with the maternal blood 1 to 20 dilution, but could not be obtained with the blood from the infant.

Ker.—"Blood of a fœtus aborted by a patient with typhoid fever, gave a negative serum test." No particulars given.

Griffith.—"And in one case that I recently saw in the service of Dr. Wm. Pepper, in the Hospital of the University of Pennsylvania, a child born at term, of a typhoid mother, failed to yield the typhoid reaction." No particulars given.

Hare reports two cases transferred from the Jefferson Maternity to his service. In both cases the fever began practically simultaneously with parturition. The blood of the infants did not cause the Widal, although that of the mothers did (personal communication). No record of dilutions given.

Wilson.[1]—Miscarriage during the fifth month on the twelfth febrile day. Fœtal blood negative for the Widal test. No particulars given.

Morse.—Labor at or near term on the tenth day of fever. The child was alive and did well. Widal negative on the eleventh day. Dilution not recorded.

Mahrt.—Premature birth at the seventh month during the second week of fever. Eight days after birth the maternal blood was found positive in 1 to 40 dilution while the child's blood was negative in 1 to 10 dilution.

Kirton[2] publishes two negative cases of fœtuses, æt. 6 months and full term respectively. In both these cases the mother's blood gave positive reaction.

Stengel reports a negative Widal with blood of a full-term child born during the second week of typhoid fever. The maternal blood gave a positive Widal. Dilutions not given.

Darling.—Premature labor at 7 months on the 21st febrile day. Positive Widal with mother's blood on the 10th day. Child lived two days. Autopsy negative. Cultures from spleen sterile. Blood from the heart gave a negative Widal.

There are also records of other negative observations mentioned

[1] Quoted by Morse.

[2] Quoted by Bolton.

above by Charrier and Apert, Etienne, Bolton (2 cases), and the three cases reported in this paper.

Observers disagree as to whether the agglutinating substances are present in dialyzed liquids, and it would appear from the study of the cases in which the Widal reaction was obtained with the fœtal blood, that the placenta acts more or less as a filter. This is concluded because the strength of the reaction in the fœtal blood is considerably less than that in the maternal blood in the great majority of cases. It is interesting to recall the facts as to the inheritance of immunity in the cases in which the mother passed through smallpox or vaccinia during pregnancy. Except possibly in very rare cases, the fœtus receives no immunity to smallpox either by the vaccination, or smallpox itself during the pregnancy. As there are no data to show whether the passage of the agglutinative substances is associated with lesions of the placenta, in view of the above, it would seem that these factors would be of importance in their transmission:

1. Strength of reaction in the maternal blood.
2. Length of time that the agglutinative power has been present in the maternal blood before labor.

In cases in which the presence of the Widal reaction has been demonstrated with the fœtal blood, it may be impossible to say whether it developed in response to the presence of the typhoid bacilli, or whether it was transferred from the mother through the placenta. In case the child was live-born and nursed by the mother, the possibility must also be considered that the agglutinins were transferred by the maternal milk. Aside from the experimental case of Remlinger's rabbit, the case of Bolton, of Fordyce, and the first case reported in this paper are the only observations in which there is mention as to the Widal in the fœtal blood, from which the typhoid bacilli were cultivated.

Data concerning the transmission of the agglutinins through the maternal milk are interesting but meager. Achard and Bensaude show that there is no agglutinating power to typhoid organisms in the normal milk. Two of the six cases examined had had typhoid some years before. Kasel and Mann found the milk of three women who had never had typhoid positive only in 1 to 1 dilution. The milk of three women who had had typhoid, and whose blood

was active in 1 to 50, was positive in two cases with 1 to 1 dilution, and the third was only suggestive with 1 to 12.

Widal and Sicard, in a number of experiments, were able to prove that the substances causing agglutination of typhoid organisms, could be transferred to the nursling by the mother's milk only in a single case. They inoculated a nursing mouse with the serum of an ass that was known to have very strong agglutinative power, and were thus able to maintain a fairly high agglutinative power in the mouse's blood. Examination of the blood of the suckling showed an agglutinative power three days later, it however at no time was half as marked as that of the maternal blood. On the 8th day, nursing was discontinued, and within the three following days the strength of the reaction fell from 1 to 250, to 1 to 100, disappearing on the 19th day.

Landouzy and Griffon.—The mother nursed her three months' child into the second week of a mild attack of typhoid. The child apparently was in perfect health. The serum, both of the mother and the child reacted positively to the agglutinating test. The dilution used is not noted. The case was not followed, as the child was sent away, so the duration of the reaction cannot be stated.

Castaigne.—A child was nursed by the mother, up into the second week of typhoid, and was then taken from the breast. On that day the child's blood serum gave a positive Widal of 1 to 40, falling the next day to 1 to 20 and then to 1 to 10. Five days later, there was no reaction. It was then put back to the breast, and with nursing the Widal was present, 1 to 10 in 24 hours, rising later to 1 in 50.

Courmont and Cade.—A two months' child was nursed by the mother into the second week of typhoid. Widal tests were taken three days after nursing was discontinued. The mother's blood reacted positively in dilution of 1 to 200, her milk in 1 to 30, while the child's blood agglutinated only in dilution of 1 to 10.

While these cases indicate that this power may be transferred by the milk, there are cases which show that it is not always transferred.

Widal and Sicard inoculated two guinea-pigs with typhoid cultures, and a third with serum possessing a known agglutinative power. The strength of the reaction in the blood of the third

animal was found to be 1 in 800 dilution. All three animals nursed their young. Their milk was found to cause agglutination with dilutions from 1 to 40, to 1 to 10. No agglutinative power could be noted in the blood of the young during the twenty-four days of observation.

A cat three days after parturition was inoculated with a culture of typhoid. Agglutinative power was noticed in the milk on the third day, gradually increasing in strength to 1 to 400 on the tenth day. At this time the blood reacted positively in 1 to 3000. Another cat immediately after parturition was inoculated with serum possessing definite agglutinative power, and the animal's blood was kept active in dilution 1 to 1200, while the milk reacted in 1 to 150. The young of these animals, fed with the milk possessing definite agglutinating power, at no time had agglutinative principles in the blood even in 1 to 1 dilution.

Two young cats were fed for six weeks with goat's milk that constantly caused agglutination in dilutions between 1 to 400 and 1 to 300. Their blood never possessed agglutinating power.

A laboratory boy who never had had typhoid fever drank half a liter of this goat's milk daily for three weeks without ever having agglutinins present in his blood.

Remlinger also made an interesting observation. An immunized and a non-immunized rabbit gave birth about the same time. The blood of the former caused agglutination in dilution 1 to 300, while her milk reacted in 1 to 40. None of her young showed agglutinating power. He then caused the rabbits to nurse the young of the other. The young of the non-immunized rabbit, nursed by the immunized rabbit failed to show agglutinative power in the blood. The same experiment was repeated for guinea-pigs with the same result.

Achard and Bensaude.—The mother entered the hospital on the fifteenth day of typhoid fever, with a nursing child, two months old. The child was well. The mother's milk gave a Widal of 1 to 10; the blood of the child gave no reaction.

Thiercelin and Lenoble.—The mother nursed her child, seven months old, during the first ten days of typhoid. On the 18th day her milk gave a positive Widal, but the child's blood did not react, even in 1 to 3. This case was examined too late after the cessation of nursing to be of positive value.

Charrin.—The mother's blood reacted in 1 to 50 and her milk in 1 to 30 dilution. The blood of the child, however, gave no reaction.

Castaigne.—The mother's milk reacted in dilution of 1 to 20. There was no reaction with the blood serum of the nursing child.

The following conclusions may be drawn from the above review:

1. That the typhoid bacillus may pass from mother to the child in utero.
2. The resulting disease is a fœtal septicæmia.
3. In cases of placental transmission, there are generally placental lesions of a hæmorrhagic type.
4. The child dies either in utero or soon after birth. There is no evidence that the fœtus may survive the infection in utero.
5. Placental transmission is not the rule in typhoid.
6. The Widal is not always given with fœtal blood, even though placental transmission be proven. When present it cannot be determined whether the agglutinating substances result from the presence of the typhoid bacilli, or whether they have filtered through the placenta from the mother's blood.
7. The agglutinating substances may be transmitted through the milk of a typhoid mother to the nursling. The reaction in the nursling's blood is but transient, and is always weaker than that of the mother's.

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METABOLISM IN ALBUMINURIA.

Paper I.

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The study of a series of the cases of nephritis in the medical wards of the Johns Hopkins Hospital with a view of determining if possible some of the influences governing the amount of albumin in the urine of these cases was undertaken at Dr. Osler's suggestion; whose kind interest taken in the work and his many suggestions during its progress the writer takes this opportunity to acknowledge.

In this paper is reported a preliminary series of ten cases of nephritis. It should here be emphasized that it is the albuminuria which is under consideration, and that the severity of this is measured by the amount of albumin present. The same cannot be said of nephritis. Of this the albumin is often a poor index. Although it is true that as a case of nephritis improves the albumin diminishes, yet a small amount may prognosticate no favorable course, and the severest case may have the least.

The ideal way of studying such a subject would be to apply all the methods of metabolism work, as regards nitrogenous equilibrium, etc., to keep the patient constant as regards amount of urine, nitrogen and albumin output for a stated period, and then introduce the factor the effect of which is to be studied, a new item of diet e. g., and observe the result. But is this possible? It seems to be the experience of many that these, the water, albumin, and nitrogen output, are a law unto themselves, that they vary from day to day despite the care taken to control them. Again, if such accuracy could be observed in following a case very few patients could be studied by one person, so much time must be spent on food, urine, and stools, and the cases could be studied for

but short intervals so many are the disturbing factors present in nephritis to upset these periods of equilibrium.

Such being the case it was decided to study a preliminary series of cases, following each even for months if possible and determine what the general course of the disease is, how great the variations in nephritis are, and if possible what produces them. This series ended, a few selected cases will be more carefully studied and it is hoped errors be avoided which would have been committed had the minute study preceded. This preliminary series has proven to us so instructive that its report may be justified.

Methods of work.—A series of ten cases was chosen, the cases selected to include as many as possible of the grades and varieties of nephritis.

The twenty-four hour urines were collected, a little chloroform being used to prevent bacterial decomposition. In case the day and night urines were studied separately the day extended from 5 A. M. to 9 P. M., and the night 9 P. M. to 5 A. M., that, is, the hours were chosen when as a rule the patient went to sleep and awoke. If there was even a suspicion that a little was lost the specimen was discarded. At each of these hours the patient was required to empty his bladder. The nephritics of a free hospital ward are seldom very intelligent, and still more rarely take the same interest in the progress of the case that the chemist does, especially if walking around. Hence the relatively small number of blank spaces in the tables bears witness to the excellent assistance that the nursing staff has rendered the clinical laboratory. The urines all bear the date of the day in which the twenty-four hours ended. Since this was 5 A. M. most of the urine was secreted during the preceding day. This point is important since changes in the urine will often seem to be one day late. Notes indicating changes in diet, etc., bear the date upon which these occurred.

The routine ward diets are fairly constant. More accurate dieting was not attempted. The diet for nephritics was milk diluted with lime water, 130 ccs. of milk being given every two hours during the day. In case other diet was allowed mention will be made of it in the tables. No attempt was made to measure the water drunk except for some short intervals.

The nitrogen and albumin of the urine were very accurately

determined, the former by the Kjeldahl method, the latter gravimetrically. In the albumin determinations the procedure recommended in the last edition of Neubauer and Vogel, Analyse des Harns, was followed, except that in the last few weeks a hint given by Cohnheim (Zeitsch. f. physiol. Chemie, Bd. XXXIII, p. 455) was found most helpful and shortened the time required by about one-half. That is, to a measured quantity of urine a certain amount of saturated sodium chloride solution was added, the amount varying with the case. The advantage is that acetic acid need not be so carefully added with the certainty that in some cases a couple of drops too many will overstep the point of complete coagulation, but this point may usually be hit first trial. Another advantage is that the point sought for is not alone perfect coagulation but a precipitate flocculent enough to remain on the filter and if sodium chloride be added in almost every case as soon as a clear filtrate was obtained the same was albumin-free. This small point if learned earlier would have allowed us to make the list of cases studied fully twice as long.

Two portions were always determined and if these did not agree a third determination was then made. At first the ash was determined and subtracted but later disregarded. The reasons for this were that in a given case the error due to ash is almost a constant quantity, also that this error was so small if due care be taken in washing the precipitate that it could be safely disregarded. In another report I shall speak of the accuracy of the method. For the work at hand it was very satisfactory. The principle of this determination is very simple, and most text-books describe the method as if it were easy. But I doubt much if one following the directions usually given would arrive at results very satisfactory if he made control tests with each determination. The method as described by Huppert in the above mentioned Analyse des Harns is very good, and the success of its use will depend on the care with which the details are followed. I would certainly recommend, however, that the sodium chloride solution be added. Experiment will tell how much. Ten cubic centimeters to one hundred of urine will usually suffice. Of course due allowance must be made for the dilution in calculating the results.

Results of work.—We first will give a brief discussion of the cases taken collectively, indicating the points to which special

attention is invited. In the discussion of the separate cases those points which that particular case illustrates will be mentioned more minutely.

Albumin percentage.—The first point which attracted attention in the study of these cases is the importance of the albumin percent as the best criterion in judging the severity of and variations in the course of a case of albuminuria, and the relative unimportance of the twenty-four hour amount. This is no new point, the percentage is the figure usually given in reporting cases but in those cases studied with a view to determining the effects of diet or therapeutic measures, it is the total amount lost in twenty-four hours which is given.[1] It is clear of course that if the amount of urine can be kept constant it would be immaterial whether the percent or grams line were used but water and albumin excretion are by no means independent, an increased albumin being accompanied by a decreased urine often, and if the per-cent line be not charted many interesting things will escape notice. In a general way the amount of urea, and other bodies normally excreted, which will be found in the urine depends on the amount of such bodies or their forerunners in the blood. To a certain extent this is true as well of water, but there is always an abundance of albumin present and the question is how much of this will the kidneys allow to escape. This is, I take it, the safest way in the light of our present knowledge to express it. Reference is often made to the presence of egg albumin in the urine after ingestion of large amounts; it may be that some of the albumin in the urine is that which the kidneys excrete since it is of no use to the body; it cannot be denied that some of the albumin may represent kidney parenchyma; the diseased renal tubules may secrete an albuminous exudate, or it may be the normal proteids of the blood cannot be restrained by the diseased renal cells. In any case it is albumin which the kidneys have allowed either "voluntarily or involuntarily" to escape, and the albumins are at hand in sufficient amount always, and the question of interest is how much will each cubic centimeter of urine contain.

Inspection of Table VIII will illustrate this well. Here we have a case in which every cubic centimeter of urine during eight

[1] See Zeitsch. f. klin. Med., XLIV, p. 441, Beiträge zur Diätetik der Nierenkrankheiten, by Kaufman and Mohr. A report from v. Noorden's clinic.

days contained approximately the same amount of albumin, hence the percentage line is straight although the total amount varied much. This represents a case of truly chronic nephritis, one in which the condition of the kidneys has become quite stable. If this is not the case the percentage of albumin will vary little (Tables XI-XII), or much (Tables II, III, IV, V, et alt.), and the acuter the nephritis the more irregular this line (Tables II, XIII.) As the case becomes more and more chronic this line becomes more and more a straight line (Table IX, IV), until it is perfectly straight and then every cubic centimeter of urine however the amount may vary will have the same amount of albumin.

Importance of the temperature.—In studying the charts after the series had been completed one thing which attracted attention was the intimate relation between albumin percent and temperature. In Tables IX and II the parallelism is quite perfect. In Tables V, VI, and III quite so. Table IV shows that the rise must be above normal before any relation to albumin may be seen. In Tables XIII and X there seems no relation at all. The explanation of this may be the following: As is well known, chronic nephritis is not always simply "chronic," but has an acute process superimposed. The chronic element may be, and in many cases is the result of a similar acute process, but it is this latter which dominates the clinical picture. Two symptoms of variations in severity of this acute process may be, the rise in temperature, and the rise in albumin percent. In so many cases have these been simultaneous that their relation seems definite. If this rise is very definite a further symptom that its meaning is an increase in the acuteness of the process is the diminution in amount of urine (Table III), for diminished amount of urine, increased percentage of albumin, and fever, are three important features of acute nephritis.

In judging the results of muscular work, diet, medicines, etc. on the albuminuria attention should be paid to the point, do these measures directly influence the albumin output or indirectly by increasing the severity of the acute process?

It is true that the rises observed are sometimes slight, but should nevertheless not be disregarded on that account. Their duration is brief but that aids us in assigning a cause.

These symptoms of an acute process may superimpose them-

selves on a chronic condition of any grade of severity (Cases I, II, X.) It would seem as if the chronic condition determined the grade of the albuminuria, the acute process the temporary variations in this grade.

In the cases it may be noted that other causes for fever are present (Cases I and VII), and the rise in albumin percent may be but an illustration of "febrile albuminuria." Attention is called to the fact that the fever here is only slight, also that febrile albuminuria is due to a nephritic process be it only so severe as cloudy swelling of the renal cells. Fever, usually high, may cause this cloudy swelling; the products of metabolism following a change in diet may cause both cloudy swelling and fever or may increase the severity of an inflammatory process already present. However caused the parallelism between temperature and albumin percent is suggestive, and we believe should the physician obey the data gained with a thermometer even though the rise be one-half a degree above normal, he would treat nephritis much better.

Effect of diet on albuminuria.—In choosing the diet for a nephritic attention must be paid to the stage of his disease. It would seem from the usual diets prescribed that the profession is not rigid enough in the acuter stages and by continuing the same diet too long becomes too rigid later. Milk well diluted and not in too great amounts (Case I), is the best diet while the process is acute, but later on the addition of meat may hasten the recovery of the patient by the improvement it will bring about in his general condition.[2] The thermometer should perhaps be used more than is the rule, and should a change in diet be followed by even a slight rise in temperature it might be advisable to return to the simpler diet.[3]

In the observations we have made it is very hard to separate the direct effect of the diet on the albumin from the effect of the diet on the nephritic process. In nearly every case the latter seemed the result of the change, and in Tables II, III, V, the unfavorable result of giving eggs and sweetbreads may be observed. In less acute cases the eggs had no evident effect (Tables X, IX). If the case be quite acute (by this I mean if there be a very acute

[2] Kaufman u. Mohr, l. c.

[3] The heat value of the diet should of course be sufficient, but during the acute stages this is not much.

element present) starvation will not influence the line of albumin output much (Table II). Proteid-poor diet seemed very unsuitable (Table XIII).

As regards the superiority of white over dark meat for a nephritic I could find no evidence (Tables III and VI), although I did not make many observations considering the point already well established. Vegetables did not seem very suitable (Tables V. and XII). Carbohydrates would be expected to have no influence at all on nephritis and a little may be in some cases allowed with benefit. (Compare Tables VI and V).

Effect of muscular work.—The position of the body and the muscular work are both supposed to influence the albumin output just as it does the urine secretion (Quincke, Arch. f. exp. Path., Bd. XXXII). This is best illustrated in the cases of cyclic albuminuria in which case it is sometimes found that while flat on the back the urine is albumin-free, when in erect posture albumin is present. Those factors which govern albuminuria in such cases would be expected to have even more influence when a gross renal lesion is present. Change in blood pressure has been the reason assigned. In these cases the first day out of bed was as a rule, followed by a rise in albumin per cent. (Table V esp. Table VI and X.) Less effect is seen in Table VII, none in IX. In the last case the renal features of the case were subordinate. The rise is only temporary; compare Tables VI and VII.

Actions of diuretics.—The effect of but two were tried, diuretin, and, the best of all, water. The effect may be one of two—a rise of urine with the same percentage of albumin and solids or a rise with a diminution of these. Unless the attempt is made to remove œdema it is hard to see what advantage there is in obtaining the first result for each cubic centimeter represents the same amount of "work," and there are more cubic centimeters to excrete. I imagine such was the case figured on Table VII for the albumin present line hardly changed its general course downwards as the urine rose. See also Table VIII. If, however, increasing the amount of urine results in the excretion of a more dilute urine it is not hard to imagine that it is of benefit to the kidneys, although the total albumin is much greater than before the rise. At any rate, this is often one of the first indications in a case of acute nephritis of improvement. The effect of diuretin, or better stated

the rise which followed diuretin in Tables IV and V were of this nature; a rise in total urine and albumin but a more dilute urine.

Relation between albumin and nitrogen output.—In Tables VII, XIII, III, II, IV, V the interesting thing is observed, that nitrogen percent runs parallel to albumin percent. According to the accepted view the excretion of these two bodies are governed by very different laws, nitrogen according to the amount of nitrogenous bodies which the body needs to be rid of, and albumin according to the renal lesion. That the former is not always the case has been observed. Yet the parallelism of their percent lines indicates that there is an intimate relation (the nitrogen of the albumin itself cannot explain this parallelism). It will interest us in the future to determine if there is any evidence that this nitrogen represents bodies not normally excreted, that is, if just as an increasing renal lesion allows more albumin to escape it will also allow other nitrogenous bodies or whether the albumin output is governed in such cases by the nitrogen. (See under Day and Night Urine).

The cyclic course of albuminuria.—On this point we have not studied enough to say definitely, yet the impression gained from our longer tables is that there are waves in the progress of a nephritis, best seen in the urine, total albumin and total nitrogen lines, which rise to a maximum then slowly fall, the period of the cycle varying in different cases. In table IV this is best seen the periods being between two and three weeks long. In table VII it is suggested although not so definite. This is even better seen in the following Tables of Day and Night Urine.

Decapsulation of both kidneys for chronic nephritis.—I was particularly fortunate in that I had opportunity to follow the urine in two cases before and after the operation (cases II and VIII).

It is of course now much too early to speak of the ultimate results, for Edebohls (Med. Record Vol. 60) pronounces six months too early. In Edebohls' eight cases of over one year's duration, all of whom were cured, the albumin and casts disappeared in 1-12 months, an average of $4\frac{1}{2}$ months. These cases were followed from 1-8 years after operation. In Dr. Halsted's two cases the time since operation has been respectively two months and three weeks. And yet in each case the signs of improvement followed very soon after the operation. The first sign was subjective, each

patient "feeling better" than before operation even before the wounds were healed. The œdema then diminished, in one case completely, and the little setback in this case is not to be wondered at nor was it of long duration. In case II the urine had reached the amount voided previous to operation in four days and on the 17th day the polyuria which Edebohls considers the first sign of improvement was present. This, Edebohls found, did not occur until after the 10th day.

Case VIII has not yet shown this polyuria. The œdema began to decrease just two weeks after operation. She "feels better."

These cases will of course be followed with great interest. They are both young, and were very severe cases. Should a cure follow they have reason to look forward to long lives of usefulness and happiness rather than a very few years of travelling the "watery course to the grave."

Detailed report of cases and discussion of each.—In the tables are given the date when the twenty-four hours ended, the amount of urine in twenty-four hours, the number of grams of albumin in one hundred cubic centimeters of urine, the total amount of albumin in the twenty-four hour specimen, and the same for the nitrogen. In the temperature colums are given the highest A. M. and P. M. records. In the charts the higher of these is used.

For the days when the day and night urines were separately studied the unit used is ccs. and gms. per hour. Again we repeat, the most of the urine was voided the day before the date given, hence, changes due to walking, diet etc., will seem one day late.

In the histories of the case is given only enough to allow the reader to gain some idea of the sort and grade of the nephritis. In the remarks following are those points which are best illustrated by this case.

On the charts the black line means the amount of urine in 24 hours, the black dotted line the temperature. Red stands for albumin and blue for nitrogen, the unbroken lines representing grams in 24 hours, the dotted lines grams per litre, that is, a line parallel to the percentage line but magnified ten times for clearness sake.

In studying the results tables are not nearly as clear as charts. Those charts given are of the tables best illustrating the point under discussion.

We regret that all the charts could not be published.

Case I.—W. A. G., male, 16 years old, white, sailor. Admitted Nov. 29, 1901. Discharged May 31, 1902.

Complains of swelling of legs.

Clinical Diagnosis.—Chronic nephritis, amyloid? Tuberculosis of hip joint.

Family History.—Negative.

Past History.—No scarlet fever or other diseases of childhood. Does not use alcohol or tobacco. Trouble with right hip began when 4 years old, has had discharging sinuses ever since.

Present illness began four months before admission after a severe wetting. The following day his feet and legs were swollen to the knees and have been so until admission. He continued to work until one week ago when following another exposure to cold his face, eyes, neck also became swollen, and he went to bed and Nov. 29, 1901, entered the hospital.

Present Condition, Nov. 29, 1901.—Œdema is slight and limited to legs. Liver and spleen somewhat enlarged. Hb. 81 per cent. Urine, Nov. 30, 480 ccs., pale, yellow, clear. Sp. gr. 1008, acid. Albumin 2 gms. per 1 l. (Esbach). Hyaline and a few granular casts.

May 31, 1902, discharged, improved. There is slight œdema of legs.

This case is considered one of amyloid disease of the kidney since there is a history of tuberculosis of the hip for twelve years, the albumin is large in amount and the casts are not at all numerous. On the other hand the liver and spleen are only slightly enlarged.

CASE I.—TABLE I.

Date.	Amount of urine in 24 hrs.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1901								
Dec. 11.....	680	0.513	3.4680 gms.	....	....	98.	98.	Milk diet.
12.....	1380	0.2435	3.3603	0.96	13.33	96.8	97.2	
13.....	....	....	.....	.. .	.. .	98.6	99.2	4 raw eggs.
14.....	1570	0.2185	3.4305	0.781	12.262	97.1	97.	
15.....	1500	0.2275	3.4125	0.83	12.45	97.2	98.1	
16.....	....	....	. . . .	....	....	98.2	....	
17.....	1860	0.171	3.1806	1.45	26.97	97.7	98.6	4 raw eggs.
18.....	1100	0.5551	6.1066	....	....	97.9	99.1	2 raw eggs.
19.....	1200	0.3192	3.8304	1.2096	14.5152	96.2	98.8	4 raw eggs.
20.....	1490	0.4561	6.8078	1.27	18.98	98.2	99.2	
21.....	1760	0.2897	5.0987	0.87	15.33	98.6	98.8	

Table I is fragmentary yet it shows clearly several things. The case at first is of only moderate severity. Amount of urine normal, albumin percent not very high, temperature normal.

CASE I.—TABLE II.

(See Chart I.)

Date.	Amount Urine.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Jan. 8.....	2180	0.23	5.1012	0.930	20.3	98.1	99	Milk 3000 cc. q. d.
9.....	1770	0.337	5.9649	1.040	18.461	98.1	99.5	
10.....	2090	0.347	7.2586	0.96	20.1894	98.5	98.5	
11.....	1712	0.33	5.6856	0.86	14.723	98.6	99.7	
12.....	1612	0.46	7.4829	1.14	18.427	98.7	99.7	
13.....	2398	0.48	11.5943	1.18	28.5	98.1	99.1	
14	1213	0.60	7.4478	1.54	18.711	99.1	99.2	
15	1795	0.39	7.0167	1.14	20.7323	98.8	99.8	Milk reduced one half.
16.....	1730	0.28	4.87	0.88	...	98.7	98.8	
17.....	2000	0.28	5.644	0.92	18.76	98.4	98	
18.....	1930	0.35	6.8631	....	.	97.7	98.1	
19.....	1310	0.39	5 21	1.08	14.4519	98.6	99.2	
20.....	1597	0.39	6.182	1.16	18.7572	99.2	99.7	
21.....	735	0.60	4.4445	1.30	9.6726	99	102	1 sweetbread.
22	1520	0.67	10.2098	1.20	18.4072	100.7	101.7	
23	892	1.222	10.9076	1.74	15.5127	98.6	99.4	
24.....	450	0.49	4.4910	1.46	6.5835	97.8	99.7	All food by mouth discont., nutrient enemata q. 4h.
25.....	870	0.37	6.5598	1.36	11.8755	98	99	Albumin per mouth.
26.....	1220	0.43	5.3033	1.00	12.2976	98	98	Milk diet gradually begun.
27.....	460	....	....	1.70	7.8568	97.3	96.5	
28.....	715	....	....	1.58	11.3614	97.6	98.4	
29.....	1280	0.91	11.7248	1.52	19.3586	97.8	99	
30.....	1265	0.64	7.9938	1.28	16.4864	98.4	98.4	

The eggs had a distinct effect, the percentage of albumin rising, and as the urine did not decrease much, the total albumin also rose. There was some elevation of temperature, slight, it is true. Nitrogen percent is quite parallel to albumin percent.

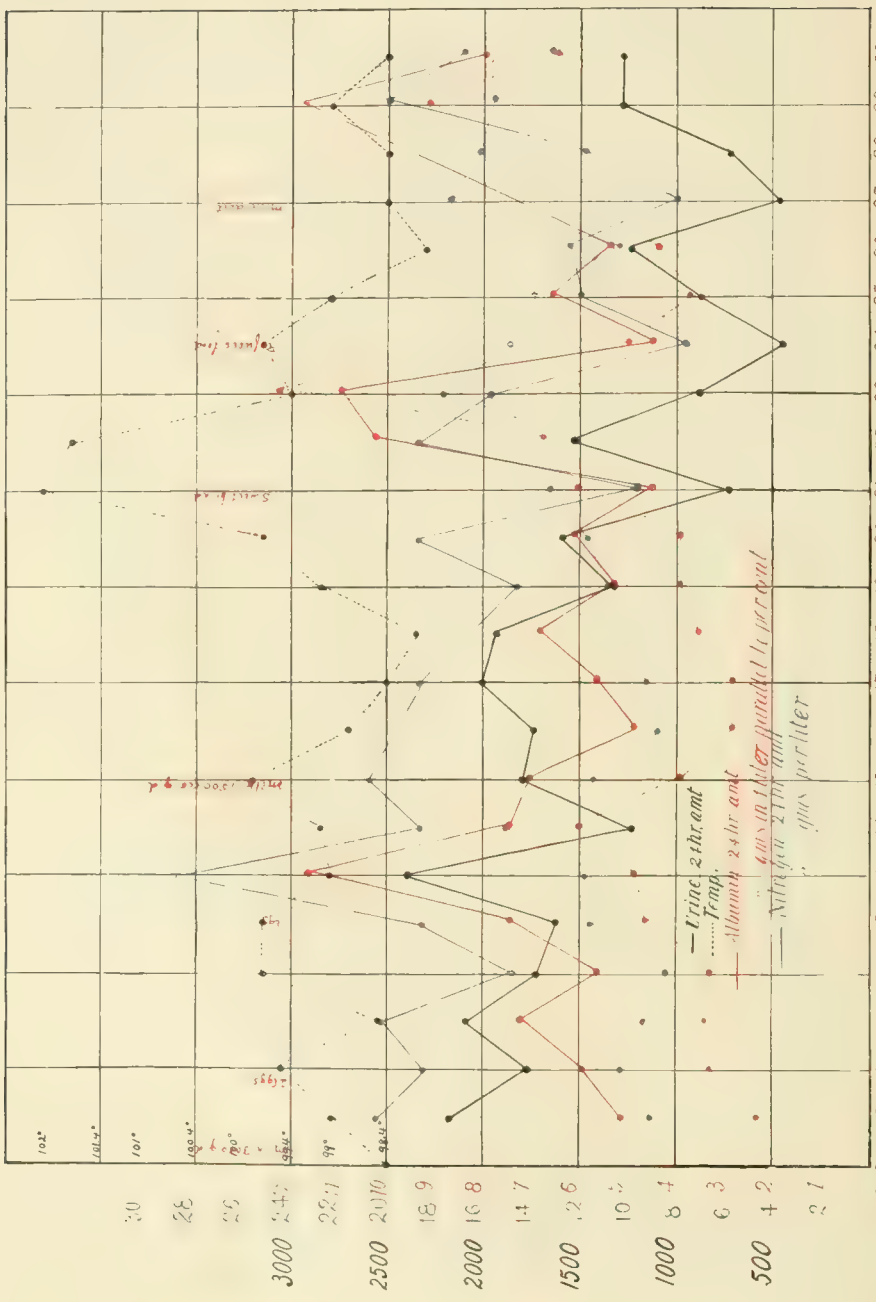


Chart I. Case I. Table II.
1902 Jan 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
— Urine 24 hr. amt
..... Temp.
— Nitrogen 24 hr amt
grms per liter

As this table is brief and fragmentary these points will be discussed in connection with better tables.

From this time on the acute element in the nephritis increased in severity. Why, is not entirely clear as the patient remained in bed on the same treatment, yet much was without doubt due to the tuberculous process in the hip; at one time (Jan. 19, 1902) the appearance was that of a new abscess about to break through the skin. Although the acute tuberculous process subsided slowly its evidences were long to be perceived.

The nephritis has become distinctly worse.

Table II, Chart I.—The amount of urine presents nothing important. The percentage line of albumin is exceedingly irregular, rising from Jan. 8 to 14, falling during the next two days; rising from the the 17th to 23rd, falling during the next two days and rising again during the next five. The attention of the reader is especially called to the parallelism between this line and the temperature line. So marked is this that one may be pardoned for insisting that the variations in both are due to the same cause, variations in severity of nephritis, and this seems to have a rather definite cycle, with six days of increasing, and two of diminishing severity.

Diet seemed to have little influence on the albuminuria except in so far as it affected the progress of the nephritis. From the albumin line alone one would not be able to say which period the patient received three litres of milk, which one and a half, which no milk at all. To the eggs can be assigned no effect. The sweetbread, Jan. 21, however, added to the already increasing severity of the nephritis and as a result we have a two day period resembling acute nephritis; scanty urine, very high albumin percentage, headache and gastric trouble. He refused to eat for three days.

The nitrogen output was remarkably high. During the period Jan. 8-15 on a diet of 2000 ccs. of milk there was on an average of 20 gms. of nitrogen. From Jan. 15-21 patient consumed 1500 ccs. of milk; the nitrogen average was 16.47 gms. From Jan. 24-27 the patient was on very low diet. Some nutrient enemata were given as he refused at first all by mouth and later could be persuaded to take but sips of albumin water. During this period the average output was 9.65 gms.

The line of nitrogen percent, and this is of importance, runs almost parallel to that of albumin percent.

CASE I.—TABLE III.—CHART II.

Date.	Amount for 24 hours.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Mar. 4.. .	1340	0.7940	10.6396	0.84	11.3498	97	97.5	Milk 1500 ccs.
5.....	1485	0.7112	10.5612	0.74	11.2266	97.1	98	
6	1580	0.6670	10.5386	0.74	11.9448	98.4	98.8	2 raw eggs.
7.....	820	1.129	9.257	1.02	8.3804	98.2	99.4	
8.....	1550	0.8983	13.9237	0.90	14.1050	98	98.4	

CASE I. TABLE III. CHART II.

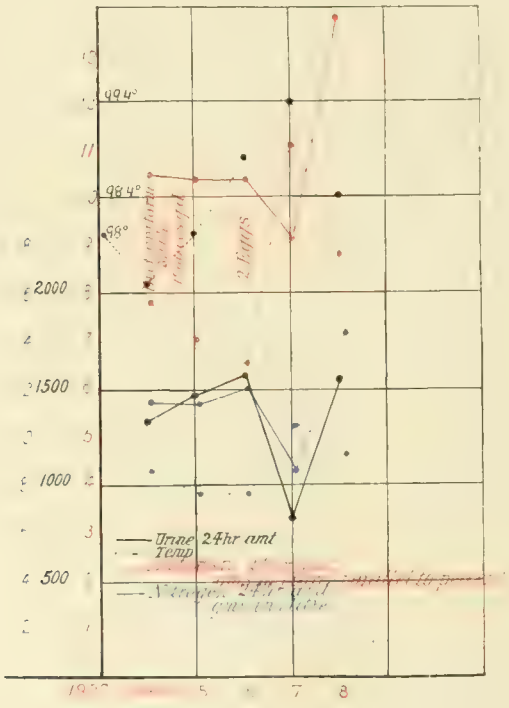


Table III, Chart II.—The patient was on constant milk diet, and in so far as possible the water was kept constant. The addition of two raw eggs was followed by a fall in total urine also in total albumin and nitrogen. Judged from these, the usual data given, the eggs had no ill effect, but the percentage lines affirm the

opposite. Their sharp rise indicates that the condition of the kidneys is more acute and each cc. of urine more pathological.

The parallelism between the albumin percent and the temperature lines is well marked. The temperature line is subnormal until the day on which the eggs were eaten (notice that the urine dated March 8 was for the most part voided March 7). The nitrogen percent line is very parallel to the albumin percent line.

Table IV contains the determinations for ten consecutive weeks. During this period the patient insists he has felt much better and clinically he has improved much. Changes in diet now cause no disturbance, his appetite is better, he is mentally more cheerful, there was progressively less œdema and finally almost none.

The line of albumin percent is still very irregular. For an explanation we look first at the temperature line to see if changes in a nephritic inflammatory process will aid. It should be borne in mind, however, that many factors may control the albumin output, and that an inflammatory recrudescence should not be assumed from a rise of temperature from subnormal to normal, and that is the case with nearly every rise during the period, and that during the periods with a distinct rise, Mar. 17, 23-30. Apr. 4-9, there are distinct waves in the percent line. On the other hand the presence of an acute tuberculous process must not be forgotten.

During this period the effect of diuretin was tried. A distinct rise in urine will be noted during the periods March 20-28, April 2-19. This may in part or whole be ascribed to the diuretin. As will be better seen in Case II, this rise in amount of urine following this drug is accompanied by a drop in albumin percent. The drop is present at these two dates and the rise which is also present during these periods has already been mentioned.

The muscular exercise involved in rolling himself in a wheel chair (perhaps position also) April 26 to May 8, and in walking, May 8, are followed in rises in the albumin percent line.

Diet seems to have had little effect on the albuminuria. The periods during the pure milk diet (March 14-23, May 14-15, 26-31) have records which give one no ground for refusing carbohydrates, or meats. No difference could be seen in the effects of dark and light meats. In the case of vegetables the rise of temperature and albumin beginning March 23 may perhaps be ascribed to this change of diet.

CASE I.—TABLE IV.

Date.	Amount of urine in 24 hrs.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Mar. 14.....	1320 ccs	0.7243	9.5594 gms.	0.868	11.4576	97.1	97.1	Milk 1500 ccs. q. d.
15.....	960	0.6799	6.5270	0.847	8.1312	97.	97.5	
16.....	1270	0.7293	9.2621	0.833	10.5791	96.6	97.2	
17.....	940	0.9418	8.8529	0.945	8.883	99.	98.4	Diuretin gr. X 3 doses.
18.....	1350	1.0542	14.2317	0.840	11.34	97.4	97.8	
19.....	990	1.0089	9.9881	0.924	9.1476	97.2	97.6	Diuretin gr. X 3 doses.
20.....	930	1.0701	9.9519	0.931	8.6583	97.	97.9	
21.....	1240	0.9828	12.1867	0.868	10.7632	97.1	97.6	Diuretin gr. X 3 doses.
22.....	2130	0.7013	14.9377	0.637	13.5681	96.	98.4	1 egg.
23.....	2000	0.6886	13.7720	0.567	11.3400	97.5	97.7	Carbohydrates.
24.....	1540	0.9896	15.2398	0.742	11.4268	97.1	98.1	Bread, butter, vegetables, q. d.
25.....	1770	0.9537	16.8805	0.728	12.8856	98.6	97.7	
26.....	1640	1.0624	17.4234	0.700	11.48	99.	98.	
27.....	2140	0.7108	15.2111	0.476	10.1864	98.6	98.	
28.....	1300	0.8758	11.3854	0.616	8.008	98.7	98.4	Diuretin gr. X t. i. d.
29.....	1190	0.9810	11.6739	....	....	98.6	98.	
30.....	1675	0.902	15.1156	0.650	10.956	97.6	97.4	
31.....	1415	0.714	10.1146	0.560	7.9548	98.1	98.2	
Apr. 1.....	1865	0.774	14.438	0.600	10.9774	98.6	97.8	
2.....	1140	0.4552	5.0072	0.364	4.0040	98.6	98.2	
3.....	2405	0.542	13.0408	0.400	9.8371	98.6	98.	
4.....	2820	0.4420	12.4644	0.371	10.4622	98.	98.2	
5.....	2410	0.440	10.6157	0.420	10.1304	98.7	98.2	
6.....	2610	0.582	15.1796	0.405	10.5896	98.2	98.8	
7.....	3040	0.751	22.8589	0.420	12.9220	98.2	99.2	
8.....	....	....	....	....	....	97.8	99.	
9.....	1600	0.6218	9.9488	0.532	8.512	98.	98.	
10.....	2050	0.480	9.8588	0.400	8.2719	98.	97.8	4 raw eggs.
11.....	1920	0.542	10.5050	0.397	7.6384	98.	97.6	
12.....	2300	0.540	12.4258	0.450	10.3565	97.4	98.2	
13.....	2180	0.5319	11.5932	0.497	10.8346	97.2	97.8	

CASE I.—TABLE IV.—*Continued.*

Date.	Amount of urine in 24 hrs.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Apr. 14	2050 ccs	0.5470	11.2135 gms.	0.4697	9.6288	98.	97.9	
15	2050	0.5854	12.0008	0.5005	10.2602	98.	97.5	Diuretin discontinued. Beef 50 gms.
16	1980	....	....	....	....	97.5	97.4	Beef 50 gms.
17	2120	0.4412	9.3534	0.434	9.3008	97.7	98.3	Chicken 50 gms.
18	2020	0.4813	9.7223	0.469	9.4738	98.4	98.4	Chicken 50 gms.
19	1130	0.5426	6.1336	0.515	5.8195	97.2	98.	
20	2020	0.6089	12.2998	0.525	10.6050	97.6	97.8	
21	1710	0.5692	9.7333	0.532	9.0972	98.2	97.8	
22	1390	....	....	....	...	98.2	98.	
23	1460	0.7030	10.2638	0.595	8.6870	97.7	98.	
24	1570	....	...	....	....	98.	98.	
25	. .	....	...	...	....	98.1	98.	
26	2130	0.5682	12.1027	0.483	10.2879	98.5	98.	Up in chair.
27	1460	....	...	.. .	....	98.2	97.	
28	2070	....	. ..	...	...	98.	98.	Light diet.
29	...	....	....	...	..	97.7	98.1	
30	1970	. .	....	....	. .	98.6	97.8	
May 1	1360	....	....	...	...	97.7	97.8	
2	1940	0.8138	15.7877	0.672	13.0368	97.	96.6	
3	1220	0.7154	8.7328	0.553	6.7466	97.6	97.8	
4	1670	....	...	....	....	97.1	97.6	
5	1590	....	....	....	....	97.	98.4	
6	1810	0.6428	11.6347	0.427	8.5432	97.6	98.	
7	1640	0.7068	11.5915	0.537	8.8068	98.4	98.4	
8	2440	0.4428	10.8043	0.364	8.8816	97.2	98.	On feet.
9	1870	0.7270	13.5949	0.553	10.3411	97.7	98.4	Chicken discontinued. Beef 50 gms. q. d. 3 days.
10	990	0.9059	8.9684	0.714	7.0686	97.8	97.5	
11	1750	0.6642	11.6235	0.602	10.5350	98.	97.7	
12	2100	0.6052	12.7092	0.546	11.4660	97.	98.5	
13	2230	0.4852	10.8200	0.413	9.2099	97.7	98.	
14	2600	0.6107	15.8782	0.518	13.468	98.	98.4	Milk alone, 1500 cc. q. d.
15	1130	0.7754	8.5294	0.525	5.775	97.1	97.6	Milk alone, 1500 cc. q. d.

CASE I.—TABLE IV.—*Continued.*

Date.	Amount of urine in 24 hrs.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
May 16.....	1800 ccs	0.6842	12.3156 gms.	0.532	9.576	97.9	98.1	Beef 50 gms. q. d.
17.....	1590	0 746	11.8755	0.573	9.1147	99.	97.9	
18.....	1350	....	....	....	....	97.8	97.9	
19.....	1600	....	....	....	....	97.1	97.9	
20.....	1770	0.761	13.4718	0.493	8.7199	97.6	98.4	
21.....	1490	0.888	13.2367	0.592	8.8192	97.	98.	Beef discontinued.
22.....	2540	0.577	14.6767	0.471	10.9696	97.9	98.1	
23.....	1740	0.742	12.9274	0.552	9.5970	97.6	98.4	
24.....	1920	0.585	11.2472	0.431	8.2796	98.6	98.4	
25.....	2020	0.514	10.3899	0.427	9.6398	97.6	97.9	
26.....	2000	0.440	8.8084	0.458	9.1609	98.	97.	Pure milk diet.
27.....	2460	0.528	12.9919	0.409	10.0702	97.6	96.5	" " "
28.....	1680	0.604	10.1447	0.629	10.5756	98.	96.4	" " "
29.....	1350	0.7876	10.6326	0.700	9.450	97.6	97.9	" " "
30.....	1430	0.6107	8.7259	0.700	10.010	97.3	98.	" " "
31.....	1200	0.7396	8.8752	0.567	6.804	97.6	98.4	" " "

Concerning the differences in day and night urines reference will be later made.

Here also the parallelism between nitrogen and albumin curves is noticeable.

In this table particular attention is called to the peculiar cyclic process in the disease, noticed especially in the lines of urine, total albumin and total nitrogen. The first cycle begins March 15, ends April 2, lasting 18 days. The second from April 2-19, a period of 17 days, the third April 19 to May 3, or 14 days; a fourth May 2-15, of 13 days; a fifth, May 15-31, of 16 days. These cycles on charts are even strikingly clear, and seem to bear no relation at all to dietetic or therapeutic measures.

In connection with this case it will be noted that although the patient felt better during the latter half of this period and clinically was better, the œdema subsiding, the temperature not rising above normal and diet affecting neither albumin nor temperature, yet the albuminuria was worse. In table I its usual level of per-

centage was 0.2 to 0.3 per cent. Table II, 0.2 to 0.4; Table III, 0.6 to 0.8, and in this table it seldom fell below 0.5 per cent, and several times crossed the 1 per cent line. The chronic process, that is, the result of previous acute processes had, we think, become more pronounced, and the lesions of the chronic nephritis for the most part determine the albumin output. The effect of the acute element of the nephritis causes variations in the albumin line waves, that is on a line whose elevation is determined by the chronic lesions.

Second admission, June 5, 1902. Returned after five days. His legs and abdomen have become more and more swollen in spite of active purgation.

Status præsens, June 5.—Œdema of legs slight. Considerable ascites.

Urine 3350 ccs. Sp. gr. 1007, acid, no sugar; finely granular hyaline and waxy casts; albumin abundant.

June 17, urine—total, 1400.

Albumin, per cent	0.6241
Albumin, total	8.7374
Nitrogen, per cent	0.399
Nitrogen, total	5.586

Casts very scarce.

June 23.—The patient is still in the wards. As will be seen the urine has not changed much. Question of operation now under consideration.

Case II.—Charles H. L. Age 21, laborer, white.

Patient was first admitted May 3, 1901 and discharged May 11, 1901.

Family History negative. Clinical Diagnosis.—Acute Nephritis.

Past History good. Has had measles, no other diseases of childhood, and "inflammatory rheumatism" when ten years old. He is a hard factory worker, a heavy eater; does not use alcohol at all, denies lues.

Present illness began suddenly (in April 1901) with severe abdominal pain and vomiting. The abdomen soon began to swell, and later the feet. The neck is also badly swollen at times. No pain since onset.

Condition on May 3, 1901. Anæmic, considerable ascites, legs, feet and neck swollen. Arteries not palpable.

Urine on admission 2000 ccs. in 24 hours, sp. gr. 1025, acid, large amount of albumin, hyaline, granular casts, pus cells and red blood corpuscles in sediment.

May 7, red blood corpuscles 4,800,000.

Discharged May 11, 1901, improved—no œdema, no ascites. Urine 3150 ccs., sp. gr. 1012. Albumin 0.1 per cent (Esbach), a few granular casts.

Temperature normal while in ward.

Second Admission.—Admitted Jan. 17, 1902, complaining of dropsy. Since leaving hospital patient has worked at intervals but has been much troubled with swelling of the abdomen and legs and with nausea. He has had much headache, "blindness," orthopnœa. Increased frequency of micturition, must rise twice at night.

Present Condition.—General œdema of body especially marked in the face neck and feet, also arms and back. Considerable right-sided pleural effusion, considerable ascites.

Urine, 1240 ccs., sp. gr., 1015, considerable albumin, no sugar; hyaline and granular casts.

Jan. 17.—Abdomen tapped, 2250 ccs. obtained.

Blood.

Red blood corpuscles	4,256,000
Leucocytes	9,000
Hæmoglobin	62%

Jan. 28.—Œdema of body now absent.

CASE II.—TABLE V.

Dat .	Amount in 24 hours.	Albumin. Per cent.	Albumin. Total.	Nitrogen. Per-cent.	Nitrogen. Total.	Temp. A. M.	Temp. P. M.	Remarks.
1902								
Feb. 16.. ..	....	....	.....	....	.....	98.4	98.6	
17.....	1940 ccs	0.538	10.4527	0.7910	15.3450	98.4	98.4	Milk 1500 ccs. q. d.
18.....	1420	0.5684	8.0713	0.938	13.3196	97.2	98.2	
19.....	....	....	.....	....	....	98.2	98.4	Diuretin gr. x, 3 doses.
20	2825	0.4146	11.7125	0.560	15.820	97.4	98.8	
21.....	3790	0.4255	16.1265	0.546	20.6934	98.7	98.4	
22.....	5050	0.3585	18.1043	0.378	19.089	98.4	98.1	
23.....	4730	0.3301	15.6137	0.385	18.2105	98.6	98.1	Told to drink less water.
24	1700	0.4626	7.8642	0.560	9.520	98.6	98.4	
25	2550	0.2270	5.7885	0.420	10.710	98.7	98.7	2 eggs – raw.
26	3640	0.2418	8.8015	0.469	17.0716	98.5	99	
27.....	3125	0.2926	9.1438	0.245	15.3125	97.3	98.4	
28.....	2740	0.5423	14.8590	0.651	17.8374	98.4	99.4	
Mar. 1.....	2000	0.8277	16.5540	0.882	17.64	98.6	99.1	4 eggs.
2.....	1625	0.6779	11.0159	1.008	15.9264	98.4	98.4	
3.....	1810	0.6222	11.2618	0.973	17.6113	98.6	.4	Total liquids (milk and water) 2590
4.....	2125	0.5069	10.7716	0.672	14.280	98.6	99.2	3150
5... .	1760	0.6274	11.0000	0.714	12.5664	99	99.8	2100 1 sweetbread.
6.....	2080	0.9258	19.2566	0.875	18.2000	98.2	98.6	3140
7.....	1835	0.8172	15.8536	0.791	15.3454	98.2	97.4	1240
8.....	2120	0.6044	12.78	0.756	16.0272	..	..	2400

Table V.—The most noticeable thing at first glance is the polyuria which may have been due to the thirty grains of diuretin. The fall in albumin percent under these conditions has been noticed in the discussion of Table IV. The rise in albumin percent beginning Feb. 26 is quite parallel to the temperature curve, also that beginning Mar. 4. In fact the similarity in the lines is quite striking (again we would mention, the albumin changes will always seem to come one day late). The two eggs of Feb. 25 may explain that febrile disturbance, the four of Mar. 1 seemed to have little effect. The sweetbread of Mar. 5 was followed by a sharp rise in albumin. As the albumin percent and temperature had begun to rise together previously the natural conclusion is that the sweetbread only intensified the rise in the albumin curve, rendering the febrile event of whatever nature it may be more intense since the maximum in temperature accompanied the digestion of the sweetbread.

The importance in watching the temperature was not realized until the cases were charted, hence many changes in diet seem poorly timed.

Again the lines of albumin and nitrogen percent run parallel.

Table VI.—Unfortunately for two successive days some of the urine was lost hence the break in the records. The patient is now on more liberal diet, milk, bread and butter being allowed.

At first both temperature and albumin percent rise. In this case, however, nitrogen percent is not parallel.

Following the successful therapeutic measures employed to kill a tape-worm the albumin percent, March 23, is high but at once drops. The patient is then allowed to get out of bed and the following day to walk. On that day, March 25, the temperature rises and the urine voided that day (date March 26) shows a great increase in albumin. I think we may assume that increase in this muscular work rendered more active the nephritis with this result.

The patient now leaves the hospital to return later for operation.

Third Admission April 8, 1902. The patient returned for operation. Through the kindness of the surgical staff I was able to follow the case.

On admission the abdomen contains considerable fluid. There is some œdema of the legs which, on April 21, has disappeared.

April 22, operation, Dr. Halsted.—Decapsulation of both kidneys for chronic nephritis. Kidneys are large, the capsule thin and quite easily

stripped although with considerable hæmorrhage. Sections cut of a small piece of cortex.

After operation there was slight infection of the wounds which, however, retarded recovery little. He was discharged May 31, feeling much better and without œdema. He was confident that his condition had improved very soon after the operation.

CASE II.—TABLE VI.

Date.	Amount in 24 hours.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Mar. 13.....	....	....	.....	...	.. .	98.2	98.3	Diet: Milk, carb. hyd., butter, bread, vegetables, no meat, no eggs, no albumin, water.
14.....	1910	0.2796	5.3404	0.770	14.707	97.2	98.4	
15	1230	0.4460	5.4858	0.931	11.4513	98.5	98.8	
16.....	1710	0.3770	6.4467	0.714	12.2094	98.6	99.2	Diuretin 3 doses each gr. x.
17.....	2080	0.4654	9.6803	0.658	13.6864	98.6	98.4	
18.....	1960	0.5635	11.0446	....	.....	97.8	98.8	
19.....	1400	0.6183	8.6562	0.714	9.9960	98.8	98.6	
20.....	1770	0.6011	10.6395	0.658	11.6466	98.6	99.4	
21.....	....	....	.....	.	.....	....	....	Urine lost 2 ds.
22.....	....	....	.....	....	.....	98.4	99	Tape-worm treated.
23 ..	800	1.0052	8.0416	0.854	6.832	98.6	98.6	
24.....	1250	0.6288	7.86	0.854	10.803	98	98.1	
25.....	1680	0.6768	11.3702	0.693	11.6424	99.4	99.4	Up in chair.
26.....	1240	1.3338	16.5391	0.770	9.548	98.4	98.9	Walking.
27.....	1640	1.0516	17.2462	0.679	11.1356	98.6	98.7	
28.....	1640	1.0008	16.5131	0.693	11.3652	98.4	98.4	
29.....	1800	1.0872	19.5696	0.756	13.608	...	....	

Patient reported June 2, stated that he was feeling very well, was looking for work, and that he had no swelling of the ankles.

Table VII.—Through the courtesy of the surgical staff I was able to follow the case for the six weeks he was in the wards, excepting the most interesting part just after the operation when the the writer's illness interfered.

That the condition of the patient had considerably improved, the record of the nine days preceding the operation will show. He

is passing a fair amount of urine of quite constant composition. It may be noted, however, that the slight changes which do occur find their parallel in the temperature line.

On April 22 the kidneys were decapsulated. At once the amount of urine fell but in five days had risen to its previous height. On the eighth day after operation the albumin percent is at the maximum recorded, and during the next four weeks falls gradually but fairly constantly reaching a minimum thirty-six days after the operation. During the next three days it rose to an unexpected height but later fell. The variations in the line of albumin percent are hard to explain. Too much information should not be demanded of the temperature line for the infection of the lumbar wounds

CASE II.—TABLE VII.

Date.	Urine in 24 hours.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Apr. 13.....	3910	0.4156	16.2499	0.378	14.7798	99	97.8	Milk 1 l. Bread. Coffee 400 ccs. Oatmeal 200 gms. Potato 200 gms.
14.....	4010	....	.....	....	.....	98.2	97	
15.....	3670	....	.....	....	.....	....	....	
16.....	3830	0.3440	13.1752	0.3885	14.8796	....	97.4	
17.....	3920	....	.....	....	.....	....	....	
18.....	4160	....	.....	....	.....	....	...	
19.....	3410	0.455	15.5201	0.43	14.7064	98	98	
20.....	2520	0.3738	9.4207	0.490	12.3705	98	98	
21	2710	0.429	11.6401	0.527	14.1309	99.2	98.6	
22.....	2500	0.5360	13.4070	0.509	12.7296	....	....	Operation.
23	740	....	.....	....	.....	....	....	Milk diet begun.
24	1030	....	.....	....	....	....	....	Milk 550 ccs., water 800.
25.....	1380	....	.....	....	.....	...	....	Milk 900 ccs., water 800.
26.....	2070	. .	.....	....	. .	....	....	Milk increased slowly to 1500 ccs. q. d.
27.....	4040	....	.....	...	.....	. .	....	
28.....	3680	....	.....	...	.....	100	....	
29.....	3820	0.6159	23.5274	0.504	19.2528	100.2	102.5	
30.....	3390	0.5776	19.5806	0.378	12.8132	98.2	100.3	
May 1.....	3460	....	.....	....	.....	99.2	100.1	

CASE II.–TABLE VII.–*Continued.*

Date.	Urine in 24 hours.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
May 2.....	3920	0.4906	19.2315	0.308	12.0736	99.2	99.8	
3.....	3880	0.5412	20.9986	0.3003	11.6516	99.5	100.5	
4.....	3720	0.4514	16.7921	0.315	11.7180	99.2	100	
5.....	3370	0.4602	15.5087	0.329	11.0199	99.4	98.8	
6.....	....	0.2842	...	0.259	. ..	99.6	100.6	
7	4120	0.3063	12.6196	0.231	9.5172	99.4	100	
8	4170	0.4086	17.0386	0.343	14.3031	99.2	....	
9.....	3500	0.3698	12.9430	0.385	13.475	99	99.5	
10.....	3490	0.3368	11.7543	0.336	11.7260	99.3	99.4	Chicken 50 gms.
11	4820	0.2750	13.2550	0.294	14.1708	99	99.1	" " "
12.....	4990	0.2669	13.3183	0.315	15.7185	99.2	99.5	" " "
13.....	4580	0.2859	13.0942	0.315	14.4270	99.2	99.2	" " "
14.....	4140	0.2946	12.1964	0.301	12.4614	. .	99	
15.....	4590	0.3587	16.4643	0.322	14.7798	99.8	100	
16.....	3950	0.3012	11.8974	0.322	12.7190	99.3	99.3	Chicken 50 gms.
17.....	3970	0.1870	7.4239	0.238	9.4486	....	99.1	
18.....	3680	0.1830	6.7473	0.318	11.7082	99	99.8	Up in chair.
19.....	4220	0.1946	8.2136	0.258	10.892	99	99	
20.....	4320	0.231	10.0128	0.325	14.0588	99.2	99.2	Walking.
21. .	4370	0.237	10.3708	0.276	12.0603	98.5	97.8	
22. ...	4470	0.273	12.2308	0.293	13.1224	97.8	98.6	
23.....	4400	0.313	13.8086	0.256	11.2952	97.8	99.2	
24 .	5800	0.1978	11.4740	0.1868	10.8395	99.1	99	
25 . .	6040	0.162	9.8042	0.191	11.5738	97.8	98	Soft diet.
26....	6020	0.1139	6.8612	0.181	10.9450	98.5	98.5	
27 ..	7190	0.0612	4.4030	0.146	10.5112	98.5	98.9	
28	6830	0.2076	14.1846	0.168	11.4807	98	98.9	
29....	5180	0.356	18.4450	0.2404	12.4537	98	98.9	
30. ...	3910	0.441	17.2440	0.288	11.2693	98	99.2	
31.....	4150	0.3128	12.9812	0.266	11.0390	97.9	98.2	
June 1. ..	3540	0.3176	11.2430	0.294	10.4076	97.9	...	

may explain this until the wounds were healed. Beginning May 8, however, an interesting parallelism is seen between these two lines.

Fifty grams of chicken had no effect but the liberal diet beginning May 25 may explain the rise in both curves, perhaps not. The muscular exertion of walking is followed by a rise in albumin percent again perhaps not in any way connected, but it is interesting that a much higher rise did not follow, since a similar influence in Table VI had so marked an effect.

Beginning May 18 there is a marked polyuria in part resulting from the literal obedience of the patient to the order to drink all he could, but Edebohls considers polyuria an early symptom of recovery after operation. I doubt if the fall in albumin percent is due to the polyuria. If that were the case total albumin would have more nearly reached a straight line and not fallen so sharply. See charts IV, V. The subsequent rise in albumin may, perhaps, be due to the fall in urine, the kidneys being "irritated" by the greater concentration of the solids normally excreted, but it will be noticed that the temperature had already begun to rise and that the two curves are beautifully parallel.

The albumin percent curve and nitrogen are quite parallel.

Again the rough periodicity in the curves should be noted (compare Table IV) except here the periods are from 8-10 days long.

The observations on day and night urine will be referred to later.

Fourth Admission: admitted June 9, 1902; discharged June 16, 1902.

Since leaving ward, patient had felt well until last evening when œdema returned, especially localized in face. He can give no reason for the reappearance.

Status præsens.—Œdema marked in face, especially eyelids, slight, of feet. Red blood corpuscles, 3,652,000; hæmoglobin, 52 per cent, urine, 2360 ccs.; specific gravity, 1005; acid; no sugar; albumin present; hyaline and granular casts.

June 11.—3420 ccs.; albumin per cent, 0.1263—total 4.3195—nitrogen per cent, 0.091; total, 3.1122.

June 16.—Patient has felt very well, œdema rapidly disappeared under influence of sweat baths and purges. Urine varied from 2000-7000 ccs. Discharged.

It will be noted that the albumin has fallen considerably; also the nitrogen. Patient feels well, wishes to be at work.

Case 3.—A. W. M., male, 39. Farmer, white.

Admitted February 21, '02. Discharged March 7, '02.

Clinical Diagnosis.—Pernicious anæmia; chronic nephritis.

Complains shortness of breath and stomach trouble.

Family History negative.

Past History.—Quite negative—is temperate, a hard worker, and until present illness always able to do a hard day's work.

Present Illness.—Onset 1 year ago, vomited each morning and two or three times during day; vomited after eating, with relief of pain. For four months was so weak he couldn't work, then improved.

During past 4 months increasing weakness, and shortness of breath have compelled him to stop work. During past month vomiting has returned and weakness much increased.

During past 1 year he has had to urinate 3-4 times a night. During past 6 months feet have at times been swollen.

Present condition, February 21, '02.—Very pale "nephritic facies." Maximum grade of arterial sclerosis.

Hæmoglobin 27%
Red blood corpuscles 1,532,000
Leucocytes 7,2000
Polymorphonuclear neutrophiles 83.6%
Small mononuclear neutrophiles 7.4
Large mononuclear neutrophiles and transitionals 5.2
Eosinophiles 2.2
Mastzellen 1.6

No nucleated reds seen.

Urine, Feb. 21, 2280 ccs., pale, sp. gr. 1010, much albumin, no sugar, granular and hyaline casts, leucocytes, red blood corpuscles.

Feb. 28, red blood corpuscles 1,356,000
March 6 1,320,000

Discharged March 7, '02 at his request. He died very soon after.

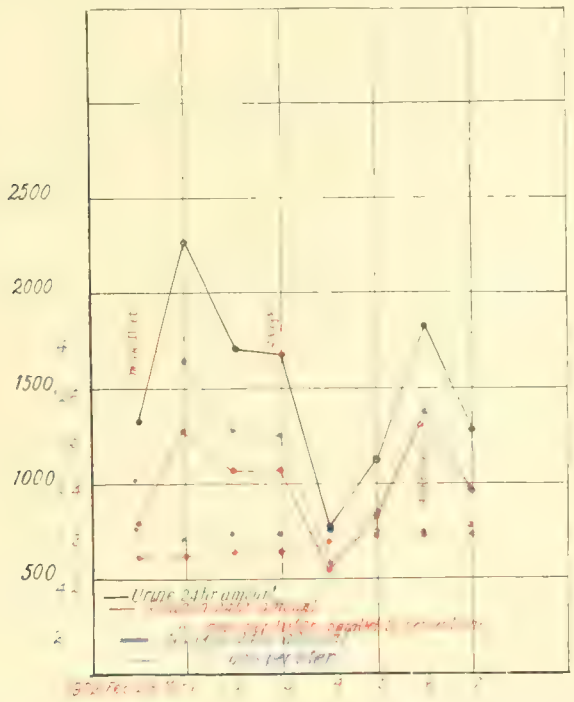
CASE III.—TABLE VIII.—CHART III.

Date.	Amount in 24 hours.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Feb. 28.....	1320	0.2402	3.170	0.625	8.2236	97.4	98.4	Milk 1500 ccs.
Mar. 1.....	2260	0.2455	5.0483	0.581	13.1306	98	97.6	
2.....	1700	0.2507	4.2619	0.609	10.353	96.6	97.8	
3.....	1675	0.2532	4.2411	0.609	10.2007	96.2	96.1	2 eggs.
4. ...	780	0.2700	2.106	0.623	4.8594	97.4	97.4	
5.....	1130	0.2850	3.2205	0.623	7.0399	98	97	
6	1825	0.2802	5.1137	0.623	11.242	97	97	Light diet.
7.....	1290	0.3000	3.87	0.616	7.9464	....	....	

Table VIII, Chart III.—In this case the nephritis may perhaps be explained by the arteriosclerosis, that is, the renal changes be entirely degenerative and an inflammatory process absent. It was the study of this case among others which convinced us of the im-

portance of even a slight rise of temperature for here it did not rise above normal, but especially of the importance of the albumin percent in judging of the course of a nephritis, for here the line is quite straight. In other words the conditions of the kidneys were stable and whether they excreted 780 ccs. or three times that amount every cubic centimeter of urine had the same albumin content. But the line, although straight, is not horizontal but slightly

CHART III. CASE III. TABLE VIII.



rises, slightly it is true, but the rise is constant, not one record being below the previous. In connection with this it is of interest that as this line rises the blood count slowly drops, a point which will receive our attention in the future.

The line of nitrogen and albumin per cent are parallel.

Here then we have the typical chronic nephritis without any inflammatory process. A renal condition so stable that the composition of the urine is unaffected by any of the previously mentioned disturbing factors.

Case IV.—P. G., male, colored. Age 56. Occupation, cook.
Admitted Oct. 26, '01. Discharged Nov. 23, '01.
Clinical Diagnosis.—Myocarditis.
Family History negative.

Past History.—Since boyhood has had occasional attacks of swelling of feet without other symptoms. This did not follow any of the acute diseases of childhood so far as he knows. Drank moderately always, heavily during past 4 years. Always heavy worker. Usual weight 250 lbs.

Present illness began one year ago with shortness of breath. Four months ago began a dry cough troubling him at night especially, dyspnœa and orthopnœa. During past 3 months symptoms increased in severity, also feet have been swollen.

During this stay in ward patient presented all symptoms of myocarditis. Urine about 1000 ccs. in 24 hours, sp. gr. 1020. No sugar. At first a faint trace of albumin with a few hyaline and granular casts. Later neither present.

Nov. 23.—Patient left hospital. For two weeks was quite well, felt faint at times, feet were swollen, pain in abdomen, troublesome cough at night, hence applied Jan. 7, '02 for readmission.

Urine on admission scanty, sp. gr. 1030, heavy cloud of albumin, hyaline and finely granular casts. The albumin was present in a trace Jan. 20, '02, just before he was discharged (Jan. 25, '02.)

After leaving hospital pain in stomach, swelling of legs and cough troubled him so that he applied for readmission March 2, '02.

March 3.—Gallop rhythm of heart present. Urine 600 ccs. Sp. gr. 1010, albumin 1.5 grms. per 1 l (Esbach), hyaline and granular casts present.

The following table contains the further urinary examinations.

The patient was discharged April 7, '02 much improved. He received the Schott bath treatment in the ward. He received thyroid extract constantly which reduced his weight from 223 lbs. to 179½ lbs.

Table IX, Chart IV.—This is a case of myocarditis with slight, yet probably very chronic, and important, renal features. The albuminuria was very slight indeed 0.8 gms. per 1 l. being the highest record. Here especially is the parallelism between the albumin per cent and temperature line evident. Here it is almost perfect and the study of this case led us to study the temperature curve of the others. Our idea of this case is of a chronic nephritis with a superimposed acute process.

Here there is no relation between the nitrogen and albumin output, nor is this surprising for the former is so slight it would hardly be expected to influence the latter much if indeed they have any relation one to the other.

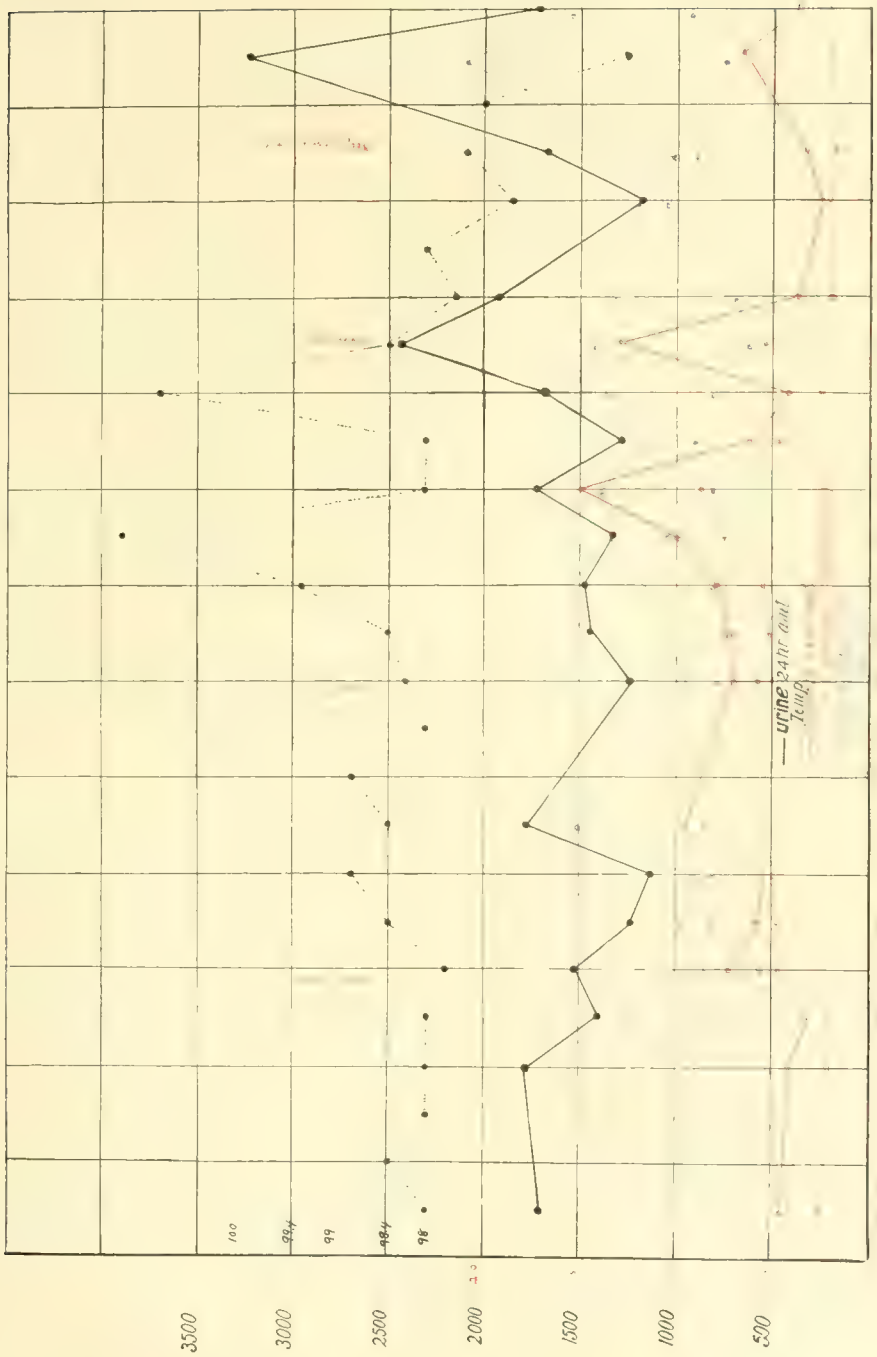


Chart IV. Case IV. Table IX.

Two attempts with raw eggs were made but the disturbance following each may not have been, or only in part may have been, a result. The rise of temperature and albumin per cent following was rather tardy and lasted rather long. Also one hundred grains of beef a day had no effect.

CASE IV.—TABLE IX.—CHART IV.

Date.	Amount in 24 hours.	Albumin.		Nitrogen.		Temp.		
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Mar. 14.....	1700	0.0255	0.4624	0.490	8.330	98	97.8	Diuretin gr. X t. i. d.
15.....	1500	....	.....	....	.	....	...	
16.....	2700	....	.....	....	....	97.8	98	
17.....	1760	0.0233	0.4101	0.399	7.0224	98	98	
18.....	1400	0.0233	0.3262	0.350	9.8000	98	98	
19.....	1510	0.0481	0.7263	0.434	6.5534	97.6	97.8	6 raw eggs.
20.....	1220	0.0491	0.5990	0.630	7.686	98.4	98	
21.....	1110	0.0502	0.5572	0.637	7.0707	98.6	98.8	
22.....	1790	0.0540	0.9666	0.665	11.9035	98	98.4	
23.....	...	..	..	....	....	....	....	
24.....	.. .	....	.. ..	....	....	98	97.7	
25.....	1220	0.0576	0.7027	0.602	7.3444	98.2	98	6 raw eggs.
26.....	1430	0.0519	0.7422	0.574	8.2082	98	98.4	
27.....	1460	0.0552	0.8059	0.623	9.0958	98.8	99.3	
28.....	1310	0.0765	1.0022	0.818	10.7158	100.2	101.2	
29.....	1720	0 0883	1.5188	0.630	10.836	97.6	98	
30.....	1280	0.0486	0.6221	0.700	8.960	8	98	
31.....	1690	0.0254	0.4293	0.630	10.647	98.7	100.8	
Apr. 1.....	2430	0.0557	1.3535	0.462	11.2266	97.2	98.4	On feet.
2.....	1920	0.0203	0.3898	0.532	10.2144	97.7	97	
3.....	....	....	.....	....	....	97.4	98	
4.....	1160	0.0232	0.2691	0.819	9.5004	97.1	97	
5.....	1660	0.0209	0.3469	0.686	7.9576	97.6	97.4	Beef 100 gms. q. d.
6.....	....	..	.....	.	....	97.4	95.4	
7.....	3220	0.0211	0.6794	0.546	17.5812	....	95.8	
8.....	1710	0.0219	0.3745	0.714	12.2094	.. .	....	

It is of interest that the muscular exertion of walking was followed by no unfavorable symptom, on the contrary he seemed

benefited judging from his albuminuria. It is not strange, his renal disturbance may have been so slight that the kidneys shared in the general improvement due to exercise.

CASE V.—TABLE X.

Date.	Amount in 24 hours.	Albumin.		Nitrogen.		Temp.		
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
Mar. 13.....	1520	0.4122	6.2654	0.7090	13.6192	97.7	98.1	
14.....	2490	0.1967	4.8978	0.847	21.0903	98.4	97.4	
15.....	2640	0.1986	5.2430	0.616	16.2624	97.2	98.4	Milk diet.
16	....	....	.....	....	.....	98.2	98.8	
17	1240	0.1478	1.8327	0.875	10.850	97.2	98.4	
18.....	....	....	... ..	....	.....	97	98.8	
19.....	1060	0.1295	1.3727	1.050	11.13	97.5	99	6 raw eggs.
20	830	0.1728	1.4342	1.225	10.1675	98.2	99	
21.....	1580	0.1335	2.1093	0.987	15.5946	97.4	98.2	
22.....	1140	0.1340	1.5276	1 036	11.8104	98.2	98.4	
23.....	1040	0.0715	0.7436	1.12	11.648	97.6	97.8	
24.....	....	....	.....	....	.....	97.6	98.8	
25.....	860	0.0811	0.6975	1.141	9.8126	97.2	99	4 raw eggs.
26.....	1205	0.0686	0.8266	1.183	14.2552	97.6	98.1	
27.....	1780	0.046	0.8188	1.189	21.1642	97.6	98.4	Eggs i q. d. and toast.
28.....	975	0.0494	0.4817	1.050	10.2375	96.3	98.1	
29... ..	1140	0.0189	0.2155	1.148	13.0872	97.2	98.4	
30	1320	0.0295	0.3894	1.085	14.322	98	98	
31.....	1080	0.0314	0.3391	1.12	12.096	97.8	98	Eggs iii q. d. Upon feet.
Apr. 1.....	1425	0.0543	0.7738	1.106	15.760	97	96.6	
2	1100	0.0488	0.5368	1.176	12.936	96.8	98	
3.....	1555	0.0428	0.6655	0.98	15.239	97	97.1	
4.....	1830	0.0414	0.7576	0.616	11.2728	97	97	
5.....	2220	0.0289	0.6416	0.574	12.7428	97	98.5	
6.....	1690	0.0458	0.7740	....	. ....	96.8	98.6	
7.....	2500	0.0188	0.4700	0.630	15.75	97	97.2	
8	1820	0.0290	0.5278	0.777	14.1414	97.2	97	

Case V.—W. H. S.—Male, colored, age 42, laborer.
Admitted March 10, '02. Discharged April 8, '02.
Clinical Diagnosis.—Chronic nephritis.
Complains of pain in breast, swelling of feet.

Past History.—Denies all diseases of childhood but measles. Acute articular rheumatism twenty years ago. Has worked hard with lumber for 18 years. Denies the use of alcohol.

Present illness began nine months ago after drinking much ice water one hot July day. Headache, stiffness of hands and arms followed at once, and five days later swelling of the feet. For two months he was confined to bed—urine scanty, dark red in color.

After this illness he worked at intervals until two weeks when after exposure to cold and wet his legs and abdomen swelled, urine became scanty and his head ached.

Present condition.—Slight œdema of feet and legs, no ascites. Arteries are very sclerotic and arterial tension high.

Urine March 12, 1400 ccs., sp. gr. 1008, pale yellow color, acid, no sugar. Albumin 2 grms. per 1 l (Esbach), hyaline and granular casts.

Patient improved much in ward. Discharged April 8, 1902.

Table X.—This is a case of chronic nephritis with an acute exacerbation. The table shows clearly the urinary changes as the acute process subsides, the albumin line becoming straighter.

The six raw eggs given March 19 seemed to have an effect, an effect independent of temperature which was already elevated. Later changes in diet were indifferent. The rise, following March 31, we consider due to the muscular exertion of walking, since this so often increases the albumin, especially when the nephritis dominates in the clinical picture. In this case no corresponding changes in albumin accompanies the two rises in temperature, March 15-20, and 24-25, but these rises are slight, 99° being the highest recorded.

Here again nitrogen and albumin are independent.

Case 6.—W. P., male, white. Age 29. Occupation, painter.

Admitted November 7, '01. Discharged November 14, '01.

Clinical Diagnosis. Lead poisoning, coma, amaurosis.

Complained of painters' colic.

Personal History.—Has handled lead for years. During past six years has had four similar attacks each lasting about 2 weeks. Drinks beer in moderation. Legs have never been swollen.

Present Illness.—One week ago colic began with nausea, pain in abdomen, headache.

Present condition.—Distinct blue line on gums. Hb. 75%. No swelling of feet. Considerable arterial sclerosis.

Nov. 8, was irrational for ½ hour followed by amaurosis. Similar attack on following day.

Nov. 8, urine 830 ccs., clear, sp. gr. 1022, acid. Albumin 8 grms. to 1 l. (Esbach), many hyaline and granular casts and pus cells in sediment.

Discharged November 14 much improved.

CASE VI.—TABLE XI.

Date.	Amount in 24 hours.	Albumin.		Nitrogen.		Temp.		
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
May 13.....	....	..	.....	....	....	98.4	99.1	Milk, cocoa.
14	950	0.0859	0.8161	1.484	14.098	97.5	98.5	
15.....	940	0.0742	0.6975	1.554	14.6076	97.	98.4	
16	570	0.0675	0.4848	1.596	9.0972	98.1	98.6	
17.....	440	0.0608	0.2675	1.708	7.5152	97.6	98.6	Pure carbohydrate diet.
18.....	.. ..	....	.....	....	.. ..	97.4	98.4	
19.....	420	0.0948	0.3983	1.600	6.720	97.1	98.4	
20.....	670	0.0617	0.4136	1.388	9.2988	98.4	....	

Readmitted May 9, '02, with a similar attack which began two days ago. Urine May 11, 740 ccs., dark yellow color, clear. Sp. gr. 1026, acid, no sugar. Heavy cloud of albumin, many hyaline and granular casts.

Table XI contains the other urinary examinations. Discharged May 20, 1902.

Table XI.—This case also is one of chronic nephritis probably without any inflammatory process at this time. The slight temperature is well explained by his general condition. The albumin line is fairly straight. It falls slowly to rise a little when patient is allowed to walk.

Case 7.—J. P. H., male, white. Age 36.

Admitted May 14, '02. Discharged May 21, '02.

Clinical Diagnosis, Chronic nephritis, pharyngitis.

Complains general weakness in legs and head.

Family History negative.

Personal History.—Has had measles, malaria. Has been a hard drinker especially in last 3-4 years.

Present Illness.—Began 1 week ago, caught cold, followed by pain in head and back and night sweats, nausea, vomiting after each meal.

Status præsens.—No œdema of legs. Some pharyngitis at first resembling diphtheria. Urine 600 ccs., yellow, clear, acid, slight cloud of albumin on boiling, hyaline and granular casts in centrifugalized specimen.

Discharged May 21, '02 much improved.

Table XII.—This is another case of slight chronic nephritis probably of arterio-sclerotic origin.

The temperature may perhaps be sufficiently explained by the throat condition, nevertheless the albumin percent line is suggestively parallel.

CASE VII.—TABLE XII.

Date.	Urine 24 hours.	Albumin.		Nitrogen.		Temp.		
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902	....	....	.....	....	....	99	100.5	
May 16.....	1280	0.0482	0.6169	0.896	11.4688	100	102.5	Liquid diet.
17.....	870	0.0535	0.4655	1.330	11.5710	100	98.4	
18	960	0.0207	0.1987	1.225	11.7600	98	98.9	
19.....	810	0.0209	0.1692	1.505	12.1905	98	99	
20.....	1200	0.0306	0.3672	0.910	10.9200	98.4	98.4	

Case 8.—Mary A. S., 17 years old, white.

Admitted March 26, '02.

Complained of swelling of abdomen, legs and face.

Personal History.—Has had measles, mumps, whooping cough. When she was four years old she had scarlet fever at which time her eyes were swollen and later the rest of her body giving her an appearance similar to the present. This lasted six months.

Present Illness.—Onset Nov., '01. Attributes trouble to mental shock due to death of her father. The eyes, then abdomen, then legs became swollen. Suffered from shortness of breath. During last two weeks has become rapidly worse. Urine very scanty, burning.

Status præsens.—Body is swollen to an extreme degree, especially eyelids and conjunctivæ, face and legs. There is fluid in both sides of the chest, and much ascites.

Urine March 29, 528 ccs. Dark red, very cloudy, heavy sediment, acid, sp. gr. 1015, no sugar. Albumin 8 grms. per 1 l. (Esbach). In sediment are casts of many descriptions, hyaline, coarsely and finely granular, and blood casts, many fatty casts. Blood, pus, and epithelial cells.

March 26 .....5000 ccs. removed from abdomen.

March 27 .....800 ccs. removed from left pleural cavity.

April 6 .....3700 ccs. removed from abdomen.

April 12-14 8710 ccs. drained from needles inserted into legs.

May 1, Abdominal tapping.....3300 ccs. removed.

May 27, Abdominal tapping.....4700 ccs. removed.

June 2.—Operation. Both kidneys decapsulated by Dr. Halsted. Kidneys found large, rather soft, " appearance of large white kidney " (Dr. Halsted's note).

Through the kindness of the Surgical Staff I was enabled to follow this case after the operation.

On the second day after the operation the œdema seemed somewhat increased. Since then has diminished a little, but not much. Large amounts of fluid from the œdematous tissue escapes through the lumbar incisions.

June 14.—Patient has been feeling better but œdema only slightly less.

June 17.—Œdema very much less, entirely gone in face. Is feeling better than has since in hospital.

CASE VIII.—TABLE XIII.

Date.	Amount in 24 hours.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
April 21.....	910	1.1322	10.3030	0.665	6.0515	....	....	Milk and carbohydrate diet.
22.....	785	0.9973	7.8288	....	.....	....	....	
23.....	....	. ..	.....	....	.....	....	....	
24....	420	....	.....	....	.....	....	.. .	
25.....	1140	. .	.....	....	.....	...	..	
26.....	1050	...	... .	....	....	....	..	
27.....	790	....	. ....	....	....	....	. .	
28.....	660	1.7619	11.6285	...	.....	...	....	
29.....	540	....	.....	...	.....	....	...	
30... .	390	....	... ..	...	.... .	....	...	
May 1.....	490	....	.....	....	.....	....	....	
2....	....	....	.....	....	... ..	...	....	
3....	1460	...	.....	....	... .	...	....	
4. ...	1460	..	.....	....	.....	....	....	
5....	1430	....	.....	....	.....	98.8	99.1	
6.....	1640	....	.....	. .	. ....	98.8	98.4	
7.....	910	1.3586	12.3633	0.770	7 007	98.4	98.7	
8.....	1130	1.1514	13.0108	0.630	7.119	98.4	98.7	Milk diet.
9.....	1430	0.8900	12.727	0.483	6.9069	98.2	98.6	
10....	1060	1.0080	10.6848	0.525	5.565	97.2	97.4	
11....	850	0.8162	6.9377	0.574	4.8790	99.2	97.9	
12.....	1580	0.6946	10.9747	0.476	7.5208	98	99.2	Carbohydrate added.
13 ...	1560	0.7818	12.1961	0.469	7.3164	98.6	99	
14.....	1570	1.0181	15.9842	0.511	8.0227	98.6	98.6	
15....	1230	1.5687	19.2938	0.623	7.6629	98.4	99.3	
16.....	680	1.9419	13.2049	0.805	5.4740	98.4	99.3	
17. ...	910	1.6377	14.9031	0 742	6.7522	98.6	98.9	
18.....	610	1.831	11.1722	0.7204	4.3946	99	99.2	
19.....	740	1 462	10.8218	....	.....	98.3	99.3	Diet poor in proteid—bread, butter, rice, potatoes.
20.....	810	1.265	10.2538	0.658	5.3340	98.4	98	
21.....	820	1.362	11.1733	0.671	5.5062	98.9	98.1	
22.....	1160	1.167	13.5427	0.526	6.1040	99.1	99	
23.....	540	1.727	9.3288	0.804	4.3442	99	100	
24.	....	....	.....	....	.....	99	100	
25.....	1020	1.281	13.1447	0.594	6.0606	99.7	99.9	

CASE VIII. TABLE XIII.—*Continued.*

Date.	Amount in 24 hours.	Albumin.		Nitrogen.		Temp.		Remarks.
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902								
May 26.....	390	1.8480	7.2070	0.840	3.2704	99	99.9	Will not drink.
27....	770	1 521	11.7122	0.684	5.2668	99.5	98.4	
28. ...	300	2.170	6.5127	0.968	2.9036	98	98.4	
29.....	410	2.5836	10.5928	1.008	4.1328	98.4	97.6	
30.....	....	....	.....	. ..	.....	....	. ..	
31.....	....	....	....	....	.....	98.4	99.6	
June 1.....	440	1.1776	5.1814	0.686	3.0184	99.2	100.6	
2... .	70	2.0072	1.4050	1.099	0.7693	....	99.7	Operation. Water 25 ccs. by mouth. Salt sol. 1100 ccs. by rectum.
3....	110	1.7090	1.8799	0.791	0.8701	100.2	101.6	Water 750 ccs. by mouth. Milk 65 ccs. by mouth. Salt sol. 3000 by rectum.
4. ..	245	0.4888	1.1976	0 434	1.0633	99	99.9	Liquids 1300 cc. by mouth. Salt sol. 2250 ccs. by rectum.
5....	540	0.7228	3.9031	0.840	4 536	98.6	99.9	Water 1300 ccs. Dilute milk[1] 40 ccs.
6. ..	490	0.4298	2.1060	0.819	4.0131	98.6	98.4	Water 650 ccs. Dilute milk[1] 160 ccs.
7....	....	....	.....	....	.....	98.4	100	Dilute milk[1] 750 ccs.
8.....	760	0.8653	6.5763	1.008	7.6608	98.2	98.3	Dilute milk[1] 750 ccs. Water 300 ccs.
9.....	620	1.0064	6.2396	1.001	6..2062	98.3	98.3	Dilute milk[1] 960 ccs.
10.....	....	....	.....	....	.....	98.3	98.3	
11....	930	0.4888	4.5458	0.504	4.6872	99.4	99.7	
12.....	1330	0.6812	9.0599	0.413	5.4929	99.6	100	
13....	....	...	.....	....	.....	99.2	99.9	
14.....	500	0.9172	4.586	0.560	2.800	99.2	99.6	Casts chiefly granular, few hyaline, very few waxy, one pus, no fatty, many renal epithelial cells, many pus cells.
15.....	....	....	. ...	....	.....	...	....	
16.....	....	....	.....	....	.....	99.4	101	
17. ...	680	1.1523	7.8356	0.588	3.9984	99.4	100	Casts as above but no good waxy, many leucocytes, many r. b. c.'s.
18.....	....	....	.....	....	.....	..	....	
19.....	. .	....	.	....	.....	....	....	
20.....	680	....	.....	...	. ..	....	....	
21.....	430	....	. .	..	.....	....	...	

[1] Dilute m k - milk 2 parts, lime water 1 part.

Table XIII.—This is a severe case of parenchymatous nephritis of long standing, with an acute exacerbation of great severity. The urine before operation was often small in amount and the albumin per cent high, even 2.5 per cent May 29. Total nitrogen has been somewhat low. The patient had an elevated temperature most of the time, but this curve seems to bear little relation to the albumin per cent curve.

Diet seemed to exert a marked effect. Lowest on pure milk diet, May 7-12, the albumin per cent line rose on the addition of bread, butter and a little vegetable, and reached its maximum on a diet as proteid-free as it was desirable to use—rice, bread, butter, potato, etc.

The interest in this case lies in the fact that on June 2 the kidneys were decapsulated. As in Case II the urine falls at once and then steadily rises. The albumin per cent first falls to the lowest point observed in this case, June 4, and then rises and falls irregularly, yet on the whole remaining at a lower level than before operation, although the pure milk diet may explain much of the improvement.

One point of interest is the relation of casts which, in this case, were very numerous. Before operation hyaline granular and fatty casts predominated and the latter were an especially interesting feature so numerous and striking in appearance they were. Immediately following operation these casts were not at all numerous but attention was attracted to the beautiful waxy casts of which there were many. Later, June 14 and 17, hyaline casts are rare, granular casts by far predominate, no good waxy casts are seen, but several which look as if the transformation to waxy cast had progressed to a certain point and then stopped. This would bear out the idea expressed by Sahli in his Klinische Untersuchungsmethoden that the transformation from one kind of cast to another occurred in the tubules and depended on the time spent there, for during the two days following the operation circumstances favored the long delay of casts in the tubules hence, perhaps, the formation of waxy casts.

The percentage lines of nitrogen and albumin run quite parallel.

The slight temperature, slow subsidence of œdema, especially the number of blood and pus cells in the urine, together with the rise in albumin render the decision concerning the present result of the operation doubtful. Edebohls excludes all cases with a period since

operation of less than six months from his records, hence we may well hope the present condition will be a temporary one.

Case 9. G. C., male, white, 17 years old. Farmer.

Admission March 12, 1902. Discharged March 27, 1902.

Clinical Diagnosis.—Hæmaturia.

Complained pain in stomach and passing blood in urine.

Family History.—Negative.

Personal History.—Excellent health till present illness. None of exanthemata of childhood. Is temperate, is heavy eater, not a hard worker.

Present Illness.—Well till June, 1901, when headache, malaise, pain on left side of abdomen began lasting 3 months. He lost weight and strength, and was troubled by frequency of micturition. Sept. '01 he passed considerable blood in his urine, and since then has passed an occasional clot of blood. Pain is near umbilicus, does not radiate. No symptoms of calculus. Since Sept. has not passed blood, only an occasional clot.

Status præsens.—Aortic diastolic murmur of heart, marked arterial sclerosis. Some involvement (tuberculosis) of epididymis of each side.

Urine March 14, 540 ccs., amber color, cloudy, sp. gr. 1017, acid, no sugar, distinct cloud of albumin.

Microscopical Examination.—Well preserved red blood corpuscles.

An occasional hyaline cast, a few pus cells.

The urine contains shreds of membranous material; some are bright red. They contain blood corpuscles and degenerated epithelial cells.

The urine was repeatedly examined for tubercle bacilli always with negative results.

Cystoscopic examination.—Bladder mucosa normal. The left ureteral orifice is distinctly swollen and hyperæmic and from it extrudes a shred of mucus-like material. The swelling about the orifice of this ureter made its catheterization impossible. Exploration of left kidney advised but refused.

Discharged March 27, '02 Clinical Diagnosis.—Hæmaturia. Tuberculosis of left kidney suspected.

Table XIV.—There is a possibility that this is not a case of true albuminuria alone but that some additional process on the left side (perhaps tuberculosis) confuses the picture. At any rate the albumin line is irregular, its variations bear no relation to the amount of urine, temperature nor diet.

Case X.—M. T., female, age 17, white.

Admitted May 20.

Complained persistent nausea and vomiting.

Family History—Father insane.

Personal History.—Always weak, nervous, occasional attacks of unconsciousness and at times convulsions (description resembles hysterical attacks). Confined 5 weeks ago. During first five months of pregnancy much vomiting. During pregnancy frequent headaches, no swelling of feet. Denies all fevers of childhood.

CASE IX.—TABLE XIV.

Date.	Amount of Urine.	Albumin.		Nitrogen.		Temp.		
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
1902 Mar. 14.....	...	...	.....	...	....	98.4	99.4	Diet, milk 1500, eggs, 4.
15.....	620	0.0966	0.5989	1.554	9.6348	98.3	100	
16.....	870	0.0886	0.7708	1.491	12.9717	97.6	99.1	Milk and 8 eggs.
17.....	....	....	.....	....	...	98	99.2	
18.....	650	0.1118	0.7267	1.554	10.1010	97	98.4	
19 .	1310	0.1784	2.3344	1.393	18.2483	97.4	98.4	
20.. ...	960	0.0762	0.7315	1.407	13.5072	97	98	
21	520	0.1042	0.5418	1.82	9.464	98.2	99.1	All eggs stopped.
22	1210	0.0985	1.1919	0.966	11.6886	98.2	99.6	
23.....	...	...	.....	....	....	98.6	97.2	
24 . .	785	0.1258	0.9875	1.491	11.7044	99.1	....	4 eggs q. d. with milk.
25 ...	1260	0.0485	0.6111	0.749	9.4374	97.3	98.9	
26.....	960	0.1202	1.1539	0.819	7.8624	98	100	
27 .	....	....	.....	...	...	.	....	

Present Illness. Began 2 weeks before admission; was not strong. Following indiscretion in diet had cramps in abdomen, abdomen swollen. Since third day of illness persistent nausea and vomiting even after drinking water. Fever 103° at onset, none since.

Status præsens.—May 20, very ill in appearance, considerable retching and vomiting.

Urine brown-red color, scanty, sp. gr. 1021, acid, no sugar, small amount of albumin (0.1% Esbach). Many red blood cells, epithelial cells, pus cells. Hyaline casts, and granular.

June 2.—Found comatose, convulsive attack, clonic contraction of arms. Pupils dilated. In few minutes passed by, then stertorous breathing.

June 3.—Temperature 102°, unable to see last night was irrational, now will answer questions.

June 5, 11 P. M.—Unconscious, convulsions, four in one half hour. Pupils widely dilated.

June 17.—From June 7 on has felt better, is rational.

Table XV.—This case is of interest in many ways. The table is fragmentary since the patient was irrational or at least irresponsible so much of the time, hence on comparatively few days could the nurses be sure the specimen was a twenty-four hour amount.

Dr. Osler considers the convulsions uremic. The present illness began 3 weeks since confinement and the urinary changes suggest an acute process.

CASE X.—TABLE XV.

Date.	Amount 24 hours.	Albumin.		Nitrogen.		Temp.		
		Per-cent.	Total.	Per-cent.	Total.	A. M.	P. M.	
June, 1902	....	....	.....	....	....	101.2	101.9	Milk diet.
4.....	605	0.1978	1.1967	0.924	5.5902	100.5	99.4	
5.....	560	0 0702	0.3931	0.980	5.488	100.	99.	
6	...	....	.....	....	....	100.6	102.	
7.....	....	....	.....	....	....	100.4	100.	
8	1430	0.0242	0.3461	0.287	4.1041	99.1	99.1	
9.....	....	.. .	.....	....	...	97.5	98.4	
10.....	....	....	.....	....	....	99.	98.4	
11	2180	0.0197	0.4295	0.049	1.0682	99.4	98.4	
12.....	....	....	.....	....	...	98.3	98.6	
13.....	....	....	.....	....	....	98.3	98.6	Diet increased, bread, butter.
14.....	6290	0.1208	7.5983	0.028	1.7612	98.3	98.3	
15.....	....	.. .	.....	....	....	97.6	98.3	
16.....	. ..	....	.....	....	....	98.	98.6	
17.....	2270	. .	.	0.091	2.0657	98.3	97.6	Albumin could not be pptd. flocculent, very little present.

The small amount of albumin is good evidence of the independence of the severity of the albuminuria and of the nephritis, for the gravest symptoms of nephritis were present, yet the albumin was found in but a small amount. The albuminuria slowly subsided till diet changed when it rose again for a brief period yet with no symptoms.

The attempt was made several times later to determine the albumin, but its presence was indicated by a faint opalescence which could not be filtered.

Day and Night Urine.

The difference between the urine of night and day to which attention was first called by Quincke, Arch. f. exp. Path. & Pharm., Bd. 32, has perhaps not attracted as much attention as it deserves. It may be that its practical value is slight, and yet it is of considerable interest, throwing some light as it does on urinary excretion.

Quincke's work has been confirmed by several observers, but the most important are the contributions by Iljisch and Laspeyres. The former is written in Russian, only a short report appearing in German (Münch. med. Wochensch., 1896). He found that in liver, kidney and heart diseases which produce œdema, the urine voided per hour during the night contains more solids and is greater in amount than that during the day. Just the reverse, that is, of normal conditions, for in health the kidneys as well as the other organs concerned in metabolism rest somewhat during sleep. In renal disease even though no œdema be present the above is true; also the difference between night and day excretion is greater if during the day the patient stirs about somewhat.

Laspeyres (Deut. Arch. f. kl. Med., Aug. 16, '00), studied this point in a good many cases of heart, kidney and other diseases. I will refer only to the renal cases. Assuming the normal relation between the amount of urine excreted per hour during the day and night (q D: q N) to be 100: 50-60 (or even 100: 80-90), he found the proportion even 100: 247 in one case. This he found true in cases with cardiac or arterial disease, and in acute nephritis or chronic parenchymatous without heart lesion, the normal ratio obtained. He considers therefore that this abnormal ratio depends on the circulatory disease (organic, not functional) and not on the renal condition alone. The explanation he gives is Quincke's that during the night the kidneys have a chance to excrete the fluid of which during the day the tissues could not rid themselves owing to the circulatory disturbances.

Neither of these men studied albumin output in this regard.

Table XVI is a summary of the cases we have observed and is compiled in the same manner as those of previous observers, i. e., the average day and night output for the period was determined and these divided by the hours of the period and the ratio of these average hourly outputs reckoned. By day we mean 5 A. M. to 9 P. M. Night, 9 P. M. to 5 A. M. The patients were in bed all the time.

TABLE XVI.

Case.	Period.	Dates of Period.	Urine. Average Hourly Output.			Albumin. Average Hourly Output.			Nitrogen. Average Hourly Output.		
			Day.	Night.	D : N.	Day.	Night.	D : N.	Day.	Night.	D : N.
Case I...	1	March 30-April 12.	82.8 ccs.	105.6 ccs.	100 : 127.5	0.5615 gms.	0.5538 gms.	100 : 98.6	0.4069	0.4317	100 : 106.1
Case II ...	2	May 17-28.	49.8	105.	100 : 210.8	0.4905	0.5162	100 : 105.3	0.3526	0.4816	100 : 136.6
Case II ...	1	April 19-22.	88.3	171.6	100 : 194.3	0.4898	0.5824	100 : 118.9	0.4484	0.7889	100 : 175.9
Case II ...	2	May 18-June 1.	217.6	179.	100 : 82.2	0.5106	0.3614	100 : 70.8	0.5076	0.4483	100 : 88.3
Case VIII.	1	May 18-28.	22.1	45.4	100 : 205.4	0.3649	0.5409	100 : 148.2	0.1573	0.2851	100 : 181.2
	2	June 20-21.	15.3	38.7	100 : 255.0	.....	.....	.....	....	...	.....
Case VI...	..	May 19-20.	21.3	25.6	100 : 120.	0.191	0.126	100 : 66	0.3465	0.3081	100 : 88.8

CASE I.—PERIOD 1.—TABLE XVII.

Date.	Urine.		Albumin.			Nitrogen.		
	Per hour.	Ratio D:N.	Per-cent.	Per hour.	D : N.	Per-cent.	Per hour.	D : N.
1902								
Mar. 30 D..	59.3 ccs.		1.0352	0.6137 gms.		0.700	0.415	
30 N..	84.5	100 : 142.5	0.7720	0.6523	100 : 106.3	0.609	0.515	100 : 124.1
31 D..	52.5		0.8016	0.4208		0.616	0.3234	
31 N..	68.	100 : 129.5	0.6210	0.4228	100 : 100.4	0.504	0.3427	100 : 105.9
Apr. 1 D..	72.5		0.8580	0.6220		0.623	0.4516	
1 N..	88.	100 : 121.3	0.6362	0.5607	100 : 90.1	0.532	0.4688	100 : 103.8
3 D..	71.8		0.7278	0.5231		0.504	0.362	
3 N..	156.9	100 : 218.5	0.3722	0.5839	100 : 111.4	0.322	0.5051	100 : 139.5
5 D..	100.7		0.5148	0.518		0.504	0.5071	
5 N..	100.	100 : 99.3	0.2908	0.2908	100 : 55.9	0.252	0.252	100 : 49.7
6 D..	123.1		0.5250	0.6464		0.392	0.4826	
6 N..	80.	100 : 64.9	0.7558	0.6046	100 : 91.9	0.448	0.3584	100 : 74.2
7 D..	132.5		0.7224	0.9571		0.406	0.5379	
7 N..	115.	100 : 86.8	0.8200	0.943	100 : 98.5	0.469	0.5394	100 : 100.3
10 D..	74.3		0.5446	0.405		0.427	0.317	
10 N..	107.5	100 : 144.6	0.3928	0.422	100 : 104.2	0.371	0.399	100 : 125.8
11 D..	51.9		0.8146	0.423		0.525	0.2724	
11 N..	136.2	100 : 262.4	0.3434	0.468	100 : 110.6	0.301	0.4100	100 : 105.5
12 D..	103.		0.5970	0.6156		0.476	0.491	
12 N..	81.3	100 : 78.9	0.3962	0.3219	100 : 52.3	0.385	0.3126	100 : 63.6

In three of our cases this point has been carefuly studied (Table XVI) not alone as regards the amount of urine and nitrogen but also the albumin output and the percentage relations.

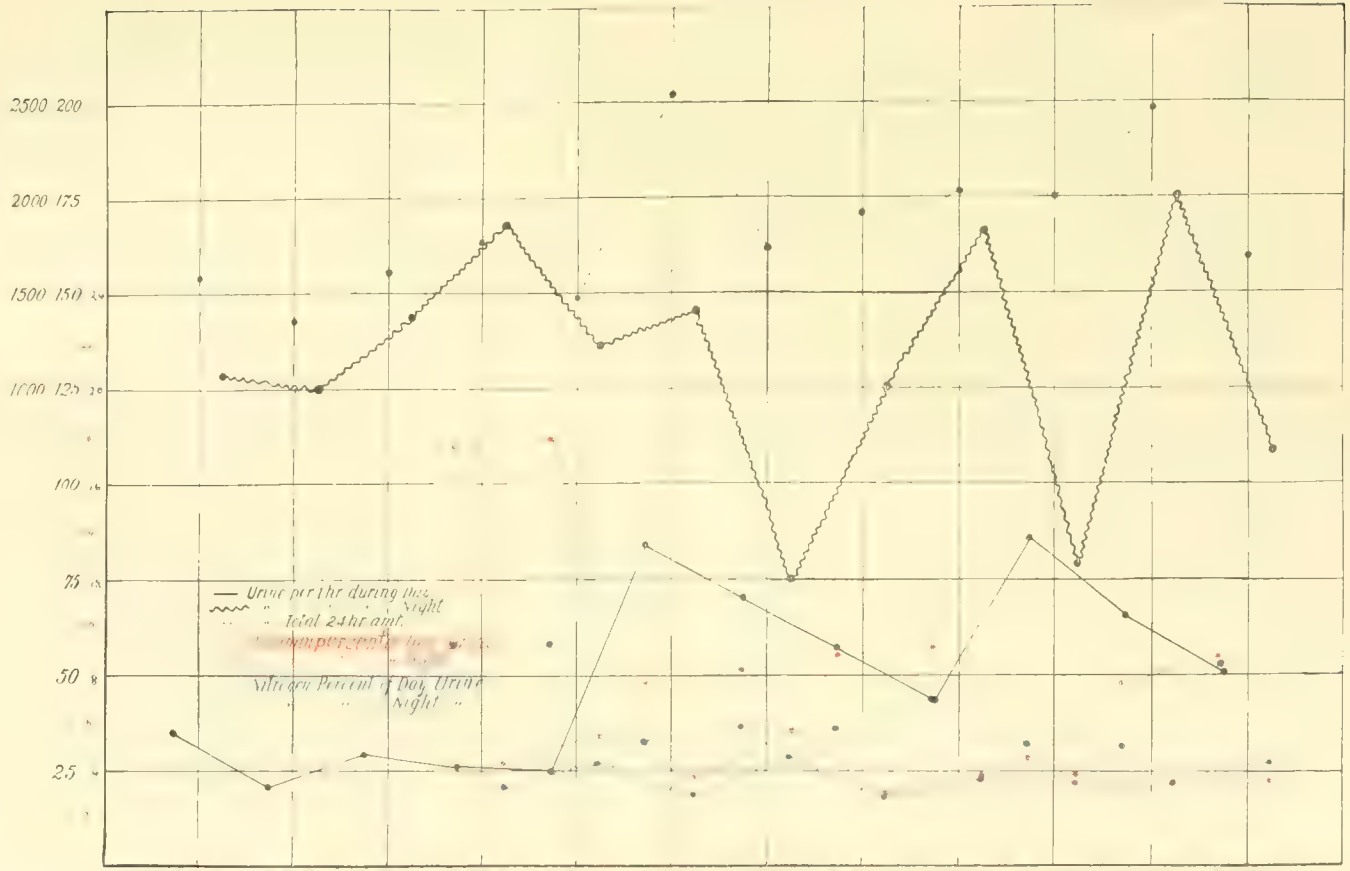
In Case I, during two periods, one of ten, the other of twelve days, the urine was studied. During each period the ratio is in favor of the night. The same is true of the nitrogen output and in period 2 of the albumin but during period 1 less albumin is lost during the night than the day. During this period the patient slept with a back rest, his body being practically no more horizontal during the night than during the day.

CASE I.—PERIOD 2.—TABLE XVIII.—CHART V.

Date.	Urine.		Albumin.			Nitrogen.		
	Amt. per hour.	D : N.	Per cent.	Grams perhour.	D : N.	Per-cent.	Grams per hr.	D : N.
1902								
May 17 D.	35.ccs.		1.4320	0.5012		0.868	0.305	
17 N.	128.7	100 : 367.7	0.3744	0.4820	100 : 96.1	0.413	0.5317	100 : 174.3
18 D.	21.8							
18 N.	125.	100 : 573.4						
19 D.	28.1							
19 N.	143.8	100 : 511.7						
20 D.	26.8		1.7643	0.4616		0.959	0.2577	
20 N.	167.7	100 : 625.8	0.4392	0.7356	100 : 159.3	0.343	0.5745	100 : 222.9
21 D.	25.		1.7957	0.448		0.959	0.246	
21 N.	136.2	100 : 544.8	0.5554	0.7567	100 : 168.9	0.448	0.6104	100 : 248.1
22 D.	86.2		0.7705	0.6473		0.536	0.4623	
22 N.	145.	100 : 168.2	0.3724	0.5397	100 : 83.4	0.308	0.4466	100 : 96.6
23 D.	71.2		0.8324	0.593		0.595	0.424	
23 N.	75.	100 : 105.3	0.5730	0.4298	100 : 72.5	0.469	0.352	100 : 83
24 D.	57.5		0.8846	0.5086		0.588	0.338	
24 N.	125.	100 : 217.4	0.3109	0.389	100 : 76.4	0.287	0.360	100 : 106.5
25 D.	43.1		0.9169	0.3954		0.693	0.2988	
25 N.	166.3	100 : 385.8	0.3807	0.5079	100 : 128.4	0.357	0.6072	100 : 203.2
26 D.	85.6		0.4624	0.395		0.511	0.450	
26 N.	78.7	100 : 91.9	0.3935	0.3099	100 : 78.4	0.343	0.2701	100 : 60
27 D.	66.2		0.7618	0.5047		0.497	0.3292	
27 N.	175.	100 : 264.3	0.3512	0.6146	100 : 101.7	0.343	0.600	100 : 182.2
28 D.	50.6		0.8606	0.4356		0.847	0.428	
28 N.	108.7	100 : 214.8	0.3648	0.3967	100 : 91	0.427	0.464	100 : 108.4

Case II is exceedingly interesting. Period 1 was before the operation and during this time the ratio is essentially that which the other observers found for such cases, more water and nitrogen being excreted in the night per hour. This is true also of the al-

Chart V. Case I. Table XVIII.



bumin, but after operation the ratio is normal for most of the time, an early symptom perhaps of recovery?

Case VIII also before the operation showed the pathological ratio in a marked degree. And although observations after operation are few there seems to have been no change.

Case VI was studied for but two days. Here only the water output is abnormal.

CASE II.—PERIOD 1.—TABLE XIX.

Date.	Urine.		Albumin.			Nitrogen.		
	Am't per hour.	D : N.	Per-cent.	Am't per hour.	D : N.	Per-cent.	Am't per hour.	D : N.
1902								
Apr. 19 D..	108.1		0.5616	0.6072		0.448	0.4781	
19 N..	210.	100 : 193.3	0.3455	0.7255	100 : 119.6	0.420	0 882	100 : 184.4
20 D..	84.3		0.4484	0.3783		0.483	0.4075	
20 N..	146.3	100 : 173.5	0.2878	0.4209	100 : 111.2	0.5005	0.732	100 : 179.6
21 D..	77.5		0.5264	0.4080		0.567	0.4398	
21 N..	183.5	100 : 236.7	0.3478	0.639	100 : 156.6	0.483	0.887	100 : 201.8
22 D..	83.1		0.6808	0.5659		0.560	0.468	
22 N..	146.3	100 : 176.	0.3720	0.5440	100 : 96.1	0.448	0.6552	100 : 140.

Study of these tables shows that the ratio is the same on scarcely two successive days. Some days it is below 100: 100 but as a rule is in favor of the night, except Table XX. But it does not do so lawlessly; there is a certain periodicity to be noted.

If these figures be charted, many interesting things may be seen.

Water Excretion.—If the night urine be represented by one line, and the amount per 1 hr. of the day as another, one would imagine that two such lines would be perfectly irregular without semblance to order. Yet when compared with each other and the line of total output they show a periodicity even more evident than that of total urine above referred to. Waves of four to seven days duration are present, the line rising to a crest then falling again.

In each case the curve of day urine is a more regular line than the night and more closely resembles the line of total urine. One reason for this is that two-thirds of the 24 hours is counted as day.

CASE II.—PERIOD 2.—TABLE XX.

Date.	Urine.		Albumin.			Nitrogen.		
	Am't per hour.	D : N.	Per-cent.	Am't per hour.	D : N.	Per-cent.	Am't per hour.	D : N.
1902								
May 18 D..	156.2		0.1644	0.257		0.280	0.438	
18 N..	147.5	100 : 94.4	0.2235	0.3297	100 : 128.2	0.399	0.5885	100 : 134.3
19 D..	206.3		0.1978	0.4075		0.252	0.519	
19 N..	115.	100 : 53.1	0.1840	0.2116	100 : 51.9	0.280	0.322	100 : 62.
20 D..	203.7		0.2519	0.5132		0.322	0.656	
20 N..	132.5	100 : 65.	0.1699	0.2251	100 : 43.8	0.336	0.4452	100 : 67.8
21 D..	195.		0.2719	0.5302		0.294	0 5733	
21 N..	156.2	100 : 80.1	0.1510	0.2359	100 : 44.4	0.231	0.3609	100 : 62.9
22 D..	190.6		0.2855	0.5442		0.280	0.534	
22 N..	177.5	100 : 93.1	0.2481	0.4404	100 : 80.9	0.322	0.5716	100 : 107.
23 D..	185.		0.3570	0.6604		0.259	0.4791	
23 N..	180.	100 : 97.3	0.2251	0.4052	100 : 61.3	0.252	0.4536	100 : 94.6
24 D..	252.5		0.2315	0.5859		0.189	0.4784	
24 N..	218.7	100 : 86.6	0.1190	0.2623	100 : 44.7	0.182	0.3982	100 : 83.2
25 D..	273.4		0.1751	0.4793		0.182	0.4982	
25 N.	207.5	100 : 75.9	0.1286	0.2688	100 : 56.	0.217	0.4502	100 : 90.3
26 D..	290.		0.1228	0.3561		0.188	0.5452	
26 N..	172.5	100 : 59.4	0.0843	0.1454	100 : 40.8	0.161	0.2777	100 : 50.9
27 D..	317.		0.0522	0.1654		0.140	0.443	
27 N..	265.	100 : 83.5	0.0829	0.2197	100 : 132.8	0.161	0.4267	100 : 96.3
28 D..	348.8		0.1870	0.6521		0.154	0.5371	
28 N..	156.	100 : 44.7	0.3001	0.4688	100 : 71.8	0.231	0.3609	100 : 67.1
29 D..	215.6		0.3145	0.6781		0.196	0.4226	
29 N..	216.3	100 : 100.3	0.4390	0.9493	100 : 139.9	0.329	0.7114	100 : 168.3
30 D..	138.1		0.5855	0.8087		0.343	0.4738	
30 N..	212.5	100 : 153.9	0.2532	0.5380	100 : 66.5	0.217	0.4612	100 : 97.3
31 D..	151.							
31 N..	215.	100 : 143.						
June 1 D..	140.							
1 N..	162.5	100 : 116.						

CASE VIII.—PERIOD 1.—TABLE XXI. -CHART VI.

Date.	Urine.		Albumin.			Nitrogen.		
	Amt. per hour.	D : N.	Per-cent.	Amt. per hour.	D : N.	Per-cent.	Amt. per hour.	D : N.
May 18 D.	14.4		2.2150	0.3184		0.812	0.1167	
18 N.	47.7	100 : 331.2	1.5994	0.7597	100 : 238.6	0.665	0.3159	100 : 270.7
19 D.	26.		1.7060	0.4478				
19 N.	40.	100 : 153.8	1.1427	0.4571	100 : 102	0.616	0.246	
20 D.	24.4		1.4142	0.3446		0.742	0.1808	
20 N.	52.5	100 : 215.1	1.1282	0.5923	100 : 171.9	0.581	0.350	100 : 168.6
21 D.	21.9		1.7931	0.3922		0.840	0.183	
21 N.	58.8	100 : 268.4	1.0420	0.6122	100 : 156.1	0.546	0.3208	100 : 175.3
22 D.	36.9		1.4194	0.5234		0.595	0.219	
22 N.	71.3	100 : 193.2	0.9067	0.646	100 : 123.4	0.455	0.3242	100 : 148.
23 D.	21.8		1.8151	0.397		0.770	0.168	
23 N.	23.8	100 : 109.1	1.5610	0.3707	100 : 93.3	0.868	0.2062	100 : 122.7
25 D.	41.3		1.2258	0.5056		0.567	0.2339	
25 N.	45.	100 : 108.9	1.4040	0.6318	100 : 124.9	0.644	0.2898	100 : 123.9
26 D.	6.9		2.0432	0.1404		0.920	0.635	
26 N.	35.	100 : 507.2	1.7716	0.6201	100 : 441.6	0.805	0.282	100 : 44.4
27 D.	18.1		2.1988	0.3985		0.924	0.1674	
27 N.	60.	100 : 331.4	1.1116	0.6669	100 : 167.3	0.538	0.3234	100 : 193.1
28 D.	8.7		2.0672	0.1808		0.938	0.0821	
28 N.	20.	100 : 229.9	2.2616	0.4523	100 : 250.1	0.994	0.1988	100 : 242.1

CASE VIII.—PERIOD 2.—TABLE XXII.

June 20 D.	20.	
20 N.	45.	100 : 225
21 D.	10.6	
21 N.	32.5	100 : 306
25 D.	8.7	
25 N.	41.9	100 : 481.6

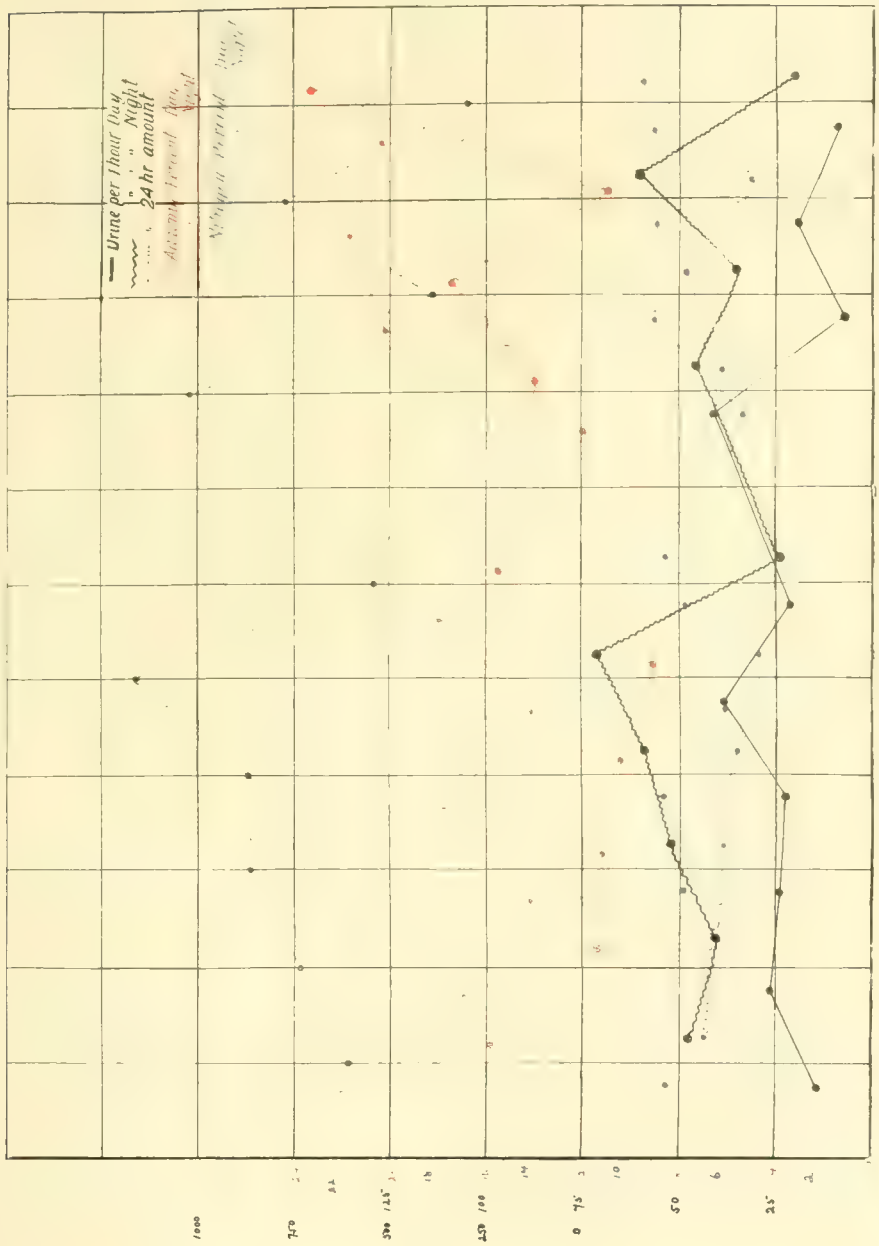


CHART VI. CASE VIII. TABLE XXI.

CASE VI.—TABLE XXIII.

Date.	Urine.		Albumin.			Nitrogen.		
	Am't per hour.	D : N.	Per-cent.	Am't per hour.	D : N.	Per-cent.	Am't per hour.	D : N.
1902								
May 19 D..	18.5		0.1022	0.0191		1.660	0.312	
19 N..	15.	100 : 81.1	0.0764	0.01146	100 : 60.	1.435	0.215	100 : 68.9
20 D..	23.8		0.0800	0.019		1.603	0.3807	
20 N..	36.2	100 : 152.1	0.0378	0.0137	100 : 72.1	1.106	0.4009	100 : 105.3

The night line is one with much more pronounced curves and with the interesting characteristic that rises and falls in the line of total urine are preceded by changes in the night urine. (Table XVIII, the reverse in XXI.)

The night and day lines are roughly parallel yet as the changes in direction of the night line preceded those of the day the lines seem running in reverse directions, as the one rises the other falls.

Table XX is interesting. Here for the most of the time the day line would be above the night line although before operation the reverse was the case. Since when he drank less water the night line assumes the upper position not by rising, but since the day line falls we may perhaps be safe in ascribing the supremacy of the day line to his drinking so much water.

According to Quincke's idea the reverse should be the case. He thinks the kidneys must make up during the night the work they were unable to do during the day, but in this case the increased work caused by increasing drink is accomplished by increased efforts during the day. It may be that water drunk may be at once excreted while the tissue fluids find greater difficulty in entering the circulation. Iljisch (l. c.) found that limiting fluid consumed during the evenings does not decrease amount of fluid excreted that night.

Albumin and Nitrogen Percentages in Day and Night Urine. —The study of these charts is particularly interesting, since it gives the possibility to study the night urine separate from the day. During the night scarcely any disturbing elements, muscular work, diet, mental excitement can affect the nitrogen and albumin output hence we can study this in its simplest condition.

The albumin per cent line for the night is somewhat straighter than for day, has fewer and less marked variations. The day line is quite constantly above the night line even when day polyuria be present (XX). In the very few cases in which the lines cross it is only a temporary affair and is due to the irregularity of the day line. The day and night lines are in some sections parallel but the parallelism is on the whole slight.

What is most interesting is the parallelism between the albumin and nitrogen percent lines. While at times this is markedly true of the day lines it is more noticeably so in the case of the night lines, and what is equally important, these two parallel lines are, especially at night but also in the day, the almost reverse of the urine lines (best seen in XXI), that is, during the night especially the albumin and nitrogen output run parallel and the percentage of each excreted varies within certain limits inversely as the amount of water.

Unfortunately during these periods the temperature effect could be seen but twice (XIX, March 22 and XVIII, April 6 and 7), and on these occasions the rise of both day and night albumin percentages was quite parallel, and the nitrogen percent lines were unaffected. These rises of temperature caused the greatest observed lack of parallelism in the albumin and nitrogen percent lines.

The nitrogen per cent lines have been quite thoroughly described above. It remains only to say that nitrogen per cent varies within certain limits inversely to the amount of urine and that this relation is much more striking than in the case of albumin, hence while the night urine line is above the day line the day percentage line will be above the night but the lines cross quite simultaneously.

Since the amount of albumin or nitrogen excreted per hour is the product of the amount of urine and percentages of albumin or nitrogen which obtained at that time it follows that these lines will show little in addition to what the urine and percent lines have already shown. It is interesting that in XX and XVII during the polyuria the total albumin fell. As a rule in polyuria the percentage may fall but the total albumin will rise since the fall in percentage is not sufficient to entirely overcome the rise in urine. Should the fall of the former be proportional to the rise of the latter the result will be a straight line. The nitrogen lines remained much straighter than the albumin.

CONCLUSIONS.

1. The percentage of albumin is the best index for the course of a case of albuminuria.

2. In many chronic cases of nephritis there is an acute process in progress, and it is this latter which governs the course of the disease. Variations in the course of this acute process are shown by (a) increase in albumin per cent; (b) slight rises in temperature.

3. The effect of various diets, therapeutic measures, muscular work, etc., on the albuminuria is often produced by their effect on this acute process.

4. In governing the diet in nephritis slight rises in temperature should be taken as evidence that the diet is unsuited to the case.

5. While the acute process is active milk is the best diet, not too much, and properly diluted. After the acute process has subsided the patient may even benefit from additions of bread and butter, rice, fruit, or even later, of meat.

6. If the day and night urines be studied separately, in addition to the points observed by Quincke, Iljisch, and Laspeyres, it was found that

a. The line of water excretion for the days is practically parallel to that of the night, but the changes in the night preceding gives the curves the appearance of being the reverse of each other.

b. The albumin per cent of day urine is practically always above that of the night.

c. In the night urine the albumin and nitrogen lines are practically parallel showing some definite relation between the excretion of these, and the percentage of each varies inversely as the amount of urine to a certain degree.

REGENERATIVE CHANGES IN THE LIVER AFTER ACUTE YELLOW ATROPHY.

By W. G. MacCALLUM, M. D.,

Associate Professor of Pathology, Johns Hopkins University.

(Plates IX–XII.)

The processes tending to a restitution to normal in the liver after recovery from some condition such as acute yellow atrophy producing great destruction of the liver substance, have recently been studied by Marchand,[1] Meder,[2] Stroebe[3] and Barbacci.[4] The results of the later of these writers are so confirmatory of those of Marchand and are so well reviewed by Barbacci that a mere summary will suffice here to indicate the nature of the facts and the views held as to their explanation, and the case here to be described will serve as a further confirmation of these views and add probably very little that is new.

There is found in these cases a more or less nodular condition of the liver, the prominent succulent nodules being sharply marked out on section from the surrounding liver substance. According to the duration of the disease there is more or less active degeneration still going on and various portions of the liver may show extreme fatty change or even actual necrosis and disintegration. Regenerative processes are evidenced in the earlier stages by the presence of mitotic figures; in the cases where the disease has been of longer duration, however, although much new formed tissue is found, karyokinetic figures are not common. The nodular masses are thought to be the expression of a regenerative activity and to be the result of a hyperplasia of liver tissue which has escaped the degenerative process. In such nodules the lobulation, though sometimes distinguishable, is much distorted and often there is a great disarrangement of the strands of liver cells. These cells,

[1] Marchand. Ziegler's Beiträge zur Path. Anatomie u. z. Allg. Path. Bd. XVII, 1895, s. 206.

[2] Meder. Ibid. Bd. XVII, 1895, s. 143.

[3] Stroebe. Ibid. Bd. XXI, 1897, s. 379.

[4] Barbacci. Ibid. Bd. XXX, 1901, s. 49.

however, are in a good state of preservation although they are often atypical in form.

The remaining liver substance shows a variety of appearances; in the earlier cases the breaking down of the tissues is still in progress side by side with regenerative changes of a second type. In the cases of longer duration the destruction of the liver cells is complete; only small pigmented masses being left to indicate their position; these lie in the meshes of a loose reticular connective tissue which is often so radiately arranged about the central veins as to preserve at least the architecture of the lobules. In this tissue regenerative changes are represented by an ingrowth of sprout from the interlobular bile ducts toward the central veins of these shadows of lobuli. Stroebe claims that a gradual transformation of the epithelial cells of such sprouts into functioning liver cells with their well known morphological characters can be observed and considers unproven the idea which Marchand puts forth that such gall ducts instead of being solely sprouts from the preformed interlobular ducts may be partly formed by a rearrangement and proliferation of the above mentioned remains of liver cells in the lobule.

These results are confirmed in the experimental work of Podwyssozki[5] and Penfick[6] who found both methods of regeneration of the liver substance after they had destroyed a portion of the liver.

The case which occurred recently in the Johns Hopkins Hospital is as follows:

Michael P., aged 13, a Polish boy, was admitted to the hospital on Sept. 17, 1901, complaining of jaundice and swelling of the abdomen. His personal history revealed the fact that he had been in the Charity Hospital in New Orleans during the winter of 1900-01 on account of a general swelling of his whole body. The records of that hospital state that he was there from Dec. 28, 1900, to March 24, 1901, and that the diagnosis was acute dysentery.

In July he was treated at this hospital for erysipelas; at that time he had no jaundice; the abdomen was full and rounded, but the physical examination was otherwise negative.

He was well according to the statements of his family up to Sept. 13, when he was taken sick with headache, vomiting and diarrhœa;

[5] Podwyssozki. Ziegler's Beiträge zur Path. Anat. u. Physiol., Bd. 1, 1886, p. 259.

[6] Pontick. Virchow's Archiv., Bd. 138, Supplementheft 1895, p. 81.

on Sept 14 he went to bed and became jaundiced. Two days later he became delirious; stools, which were passed involuntarily, were pasty, yellow and very foul; urine very deeply bile stained.

On admission he was very dull mentally. Physical examination of the thoracic organs was negative. Liver dulness decreased in extent. Abdomen much distended; spleen not palpable; very deep jaundice.

During the following days, until Sept. 27, when he died, the condition remained about the same; he was sometimes noisy; oftenest in a muttering delirium. Stools always very foul. On Sept. 23 they contained blood, and on the 27th there was an extensive hæmorrhage from the intestine, after which he died. From time to time petechial hæmorrhages were seen in the skin. On Sept. 23 the blood-count showed the following relations: Rbc., 4,850,000; Hb., 82 per cent; leucocytes, 12,700.

The urine, which was throughout of high specific gravity, contained, beside albumin and casts, leucin and tyrosin. As described above, it was deeply bile stained. The temperature while in the hospital was generally subnormal.

The autopsy was performed four hours after the boy's death. Protocol, in brief, as follows:

The body is that of a well-developed boy, 130 cm. long. Subcutaneous fat in small amount.

Peritoneal cavity contains a large quantity of bile-stained fluid. Peritoneal surfaces smooth. Blood-vessels of abdominal wall, especially those accompanying the round ligament of the liver, are much distended. Lymphatic glands of mesentery swollen: lymphatic trunks in intestinal wall and mesentery distended with a bile-stained fluid.

Pleural cavities free from excess of fluid. Pericardial cavity contains a little fluid. Serous surfaces smooth.

Heart.—Valves and endocardium generally normal. Heart muscle somewhat flecked with yellowish areas.

Lungs show no especial abnormality.

Liver is much decreased in size, and in the mammillary line reaches only to within 5 cm. of the costal margin. It weighs 620 grms. and measures 18 x 11 x 9.5 cm. The liver is much deformed by a large mass which occupies the posterior portion of the right lobe, while the left is small and tongue-like, averaging only 2 cm. in thickness, so that the extreme measurements of the liver do not give an accurate idea of its bulk. The surface of the liver is glistening and smooth, but over the mass described in the right lobe it is very uneven and nodular (Plate IX). The color of this nodular projecting portion is dark greyish green, contrasting with the grayish red of the remaining liver substance (Plate X). Such dark greenish nodular masses project also from the whole surface of the Spigelian lobe and in much smaller numbers from the under surface of the left lobe. On section they give at once the impression of a new growth in the liver. There are scattered small nodules skirt-

ing the borders of the main mass and irregular spurs of the general liver substance extend into its depths. These nodules are made up of a tissue which has in general the appearance of liver tissue, but its lobules are irregular in form, very much larger than normal and very succulent in appearance, each one having a deep green central portion with a greenish grey periphery. The portal veins and sublobular veins are readily distinguished, and there seems to be an increase in the connective tissue about these structures. In the left lobe, and indeed in all the liver tissue outside of these nodular masses, the lobulation is very indistinct. The liver substance is greyish and somewhat translucent. It is not succulent or tumid, but the cut surface tends rather to be concave and is quite smooth. The tissue is tough and leathery in consistence, and the vessels and bile ducts lie so close together as to suggest that there has been a loss of liver substance. It resembles somewhat the appearance seen in the senile atrophic liver. The gall-bladder contains thick blackish bile. Only thin, clear yellowish fluid can be squeezed through the ducts. On dissection, however, the ducts seem quite patent.

Kidneys are of about normal size; the capsule strips off readily. The striations of the cortex are somewhat irregular however, and the labyrinthine portion of the cortex shows patches of yellow opacity.

Spleen is enlarged, deep purple-red in color and quite firm in consistence. There is a deep red, very firm mass in the central portion reaching to the capsule; apparently an infarction.

The other abdominal organs show nothing of interest except the colon, in which the crests of the folds of the mucosa are covered with a greyish exudate about which are numerous hæmorrhages.

The anatomical diagnosis provisionally written was:—

Extensive atrophy of liver substance with cirrhosis. Adenomatous new growth of liver; chronic passive congestion of abdominal viscera. Chronic diffuse nephritis. Icterus. Diphtheritic colitis.

In the microscopical examination the condition of the liver was found to agree very closely with the most advanced of those described by Stroebe. There are, roughly speaking, two general types of tissue to be found, which, as we shall point out, represent the result of two different efforts at the regeneration of the liver. These types of tissue may be considered separately although in point of space they are very closely related in the liver.

The general substance of the liver which we may describe as the first type corresponds with that described macroscopically as forming the greater part of the left lobe and extending between

the nodules everywhere. Portal spaces and sublobular and even central veins could be seen but the lobulation was indistinct and the whole tissue had an atrophic appearance.

In the section it is found to be a tissue roughly lobular in structure; the portal spaces and central veins can be generally made out and the tissue seems much like the skeleton of normal liver tissue. The lobules are there, but there are no liver cells in them; the radiate arrangement is maintained by the capillaries and the intercapillary connective tissue. In the peripheries of the lobules however there are bands of cells which resemble newly formed gall ducts and indeed are easily traced into direct connection with the interlobular gall ducts in the portal space. The interlobular structure except for some proliferation of the gall ducts seems to be almost normal.

On more careful examination we find the following condition in these shadow-like lobules. The central vein is surrounded by a thick coat of newly formed connective tissue which sends out sheaths along the radiating capillaries and forms with them a pretty dense radiating network. This connective tissue is very loose and spongy and contains a moderate number of elongated vesicular nuclei and occasional lymphoid and plasma cells. (Fig. 1). The capillaries are not especially altered and keep almost their normal course. In place of the liver cell strand however, we find only the loose connective tissue. Here and there in a space in this tissue one sees shrunken masses of protoplasm with deeply staining nucleus and densely pigmented cell body which can only be the remains of the liver cells. They are quite isolated in little spaces in the connective tissue and have no connection whatever with the galls ducts about to be described.

Entering the lobule from all sides and tending toward the central vein are bulbous sprouts from the proliferating interlobular gall ducts. These extend perhaps one fourth or one third of the distance toward the central vein from the periphery. They are independent of one another except that they often arise as branches from one outlying gall duct; indeed one trunk may send several sprouts into the lobule. They are seen to push into the connective tissue between the capillaries by their blunt rounded ends which are swollen to a size much greater than that of the stem gall duct. They have a lumen resembling a wide bile capillary and continuous

with that of the gall duct. Their outline is quite smooth and in alcohol preparations they contract away from the connective tissue in which they lie leaving a clear space about them. (Fig. 1). The epithelial cells do not rigidly retain the characters of those of the ducts but become much larger; the nucleus also becomes larger, paler and more definitely vesicular; the chromatin granules are much finer and a well defined nucleolus which takes a reddish stain with hæmotoxylin and eosin, appears. In the terminal cell of one such sprout a mitotic figure was found (Fig. 2). The protoplasm becoming more granular, takes on a definite eosinophile stain and fat granules, sometimes in abundance, appear in it.

Let it be emphasized again that these sprouts have no connection with the remains of degenerated liver cells lying toward the center of the lobule; they are quite sharply outlined and do not spread out in the tissues of the lobule. In serial sections it can be definitely determined that they are compact club-shaped cell masses. We can therefore not agree, at least as far as this case is concerned, with the assertion of Marchand that they may be formed by the apposition of the degenerating liver cells which take on a new functional activity. This point of view is further contradicted here by the appearance of a mitotic figure in the tip of such a sprout showing almost conclusively that it was growing into the lobule. Podwyssozki arrives too without any doubt at the result to which we have come, in his experimental studies in which he finds a new growth of bile ducts into a granulation tissue after removal of a portion of the liver; these newly formed bile ducts progressing inward as blind tubular structures which push into the granulation tissue. Stroebe too considers the opinion of Marchand unproven.

The condition in this portion of the liver then represents obviously the result of an almost complete destruction of the liver cells probably beginning in the periphery of the lobules and proceeding toward the center since we find scattered remnants of the original liver cells near the central veins. The connective tissue structures are not destroyed but increased in bulk. Following this comes an attempt at regeneration by the ingrowth into this scaffolding of connective tissue in each lobule of sprouts from the interlobular gall ducts the more terminal cells of which become differentiated from those of the parent gall duct and come to resemble

liver cells. That they are in functional activity is at least indicated by the presence of bile in the lumen or bile capillary which retains its continuity with the interlobular gall duct.

The nodular portion of the liver microscopically proves to consist of liver cells arranged to form a tissue which has a general resemblance to liver tissue but in which the ordinary conformation of the lobule is much distorted. The lobular groups of cells have in general an arrangement into strands with intervening blood capillaries but the number of cells forming the strand varies so much and the anastomoses are so numerous and irregular that it seems as if in a greatly enlarged liver lobule the strands of liver cells had been confused together and displaced from their proper direction. The strands frequently contain five or six cells abreast and sometimes even more so that the blood supply is very distant from the more centrally placed cells. Such enlargement of the strand leads frequently to a great diminution in the size of the capillaries which become mere narrow clefts, the walls of which are almost in contact.

While the arrangement of the cells is thus distorted in the strands of the lobule, the general appearance of the lobule departs still further from the normal from the fact that the central vein is frequently found at the edge of the mass. This is due, as pointed out by Stroebe, to the atrophy of the liver cells in one half of the lobule after which the remaining half proliferates to form a large irregular mass the central vein of which is then at the extreme margin. Similarly a smaller portion of the lobule may become atrophic and the hypertrophic remainder then partly surrounds the central vein. Again the portion of the liver lobule preserved and becoming hypertrophic may be only a very small part of the periphery of the original lobule and in such a case we find a mass of liver cells at a distance from the central vein which is then surrounded by the atrophic tissue.

On the other hand, as Ponfick points out, a sort of budding of the lobule may occur; one of the tributaries of the central vein becoming widened and finally forming a secondary central vein with its own capillary tributaries and liver cell strands.

Ponfick in his experimental work found that after removal of all but one lobe of the liver in dogs the needs of the organism brought about a hypertrophy of the remaining liver substance which re-

sulted from the great multiplication of the liver cells everywhere throughout the lobule thus leading to the great enlargement of each lobule together with the marked disarrangement of the radiating strands. He considers it a true functional hypertrophy. The condition in this case must be considered as exactly analogous. As described we have an almost complete destruction of the functioning liver cells with the exception of lobules and portion of lobules here and there, and these proceeding as did the intact lobules in the small portion of the liver left by Ponfick, become hypertrophied in the same way, the process resulting here also in the production of disarranged masses of cells.

In the minuter changes occurring in such a tissue mass we again have an almost exact reproduction of the phenomena observed by Podwyssozki and Ponfick.

The cells show no karyokinetic figures as far as could be determined after study of very many sections, but they do show other indications of proliferation. They are not at all uniform in appearance, as may be seen from Fig. 3. There are some cells, relatively of smaller size, and generally possessing concave contours, which have a very dense cell protoplasm staining deeply with eosin etc., while the others are very pale and less densely granular. These latter are swollen looking, have convex contours, and correspond with those recognized by the above mentioned authors as the cells in active proliferation. Ponfick states that while karyokinesis is frequently seen in these cells during the first few days after the operation, the form and nature of the protoplasm is afterward sufficient to characterize them as young cells. Podwyssozki explains the appearance of the smaller darker cells by saying that they are compressed by the proliferating ones but it seems unnecessary to give such an explanation. In many less actively proliferating parts of the nodules they are very numerous and it seems enough to say that they are not so young or so near to the process of mitosis as the larger and more succulent ones. It is to these last that the greyish color and tumid appearance of the nodule is due.

Toward the central vein the liver cells are quite frequently enormously enlarged and contain a great many nuclei. Such cells are very deeply stained and generally contain much bile pigment in granules and small globules. It has not been apparent that the very pale cells above described contained several nuclei oftener

than the darker ones as stated by Podwyssozki and here we have the most deeply staining cells with greater bile content provided with many nuclei (Fig. 4).

About the central veins there are often some remains of degenerated liver cells; they are mere shadows in many instances but sometimes contain globules of fat as shown by the osmic fixation. The liver cells in the main mass of the hypertrophic nodules show very rarely indeed any globules of fat.

The bile capillaries are well developed throughout the nodules and ramify among the cells in each strand in the most complicated way; especially toward the central vein they are frequently distended with bile which is easily recognizable in the stained section. They are produced apparently *pari passu* with the new production of liver cells. Toward the periphery of the lobular mass their lumen can be traced into continuity with that of the interlobular gall ducts whose lining cells are continuous with the liver cells. Granular masses of bile are most abundant in the liver cells toward the central veins.

The nodular masses seen in the macroscopic cut surface of the liver are therefore made up of liver tissue arising from remnants left in the general destruction of the liver substance and brought to its present bulk by the great proliferation of the liver cells evidences of which process still remain, although no mitotic figures were found. This proliferation gives rise to great irregularity in the structure of the lobule but the general plan can often be made out or the condition explained from a knowledge of how large a part of the original lobule is concerned. The bile capillaries keep pace with the new growth of cells and retain their communication with the interlobular gall ducts the lining cells of which of course remain continuous with the liver cells.

As to the nature of the acute process which caused such extensive destruction of cells we can say nothing definite; there is only the indefinite description of a severe illness lasting three months, six months before the onset of the terminal illness and it seems probable that it was at that time that the acute process ran its course. From close resemblance of the pathological condition with that in the cases of Marchand, Stroebe and Barbacci it seems that, as there is nothing in the statement of the family to point to the possibility of phosphorous poisoning, we will not go far wrong in considering

this too a case of acute yellow atrophy of the liver in which the degenerative have given place to regenerative processes.

Ponfick states it as his opinion that the conditions produced by him in his experimental work represent true functional hypertrophy of the liver and are different from the conditions seen in pathological processes or even in those experiments of Podwyssozki in which the removal of part of a lobe of the liver was followed by formation of granulation tissue later penetrated by new formed gall ducts, from the fact that these conditions are complicated by inflammatory processes. It seems however that the essential of the process is the reproduction of liver tissue and we have quite as true functional hypertrophy no matter whence the new liver cells arise. The same principle underlies their origin in each case; where well differentiated liver cells still persist, the new liver tissue is very simply produced by their mere multiplication by division and the less highly differentiated gall ducts take no part in the process but remain quiescent in their subordinate position as conductors of the secretion of the liver cells. Where however all the fully differentiated liver cells have been destroyed the epithelial cells of the gall ducts take upon themselves the more complicated process of production of liver tissue by first rapidly multiplying and then becoming differentiated, adopting the characteristics of the liver cells.

EXPLANATION OF FIGURES.

PLATE IX. General view of upper surface of the liver.

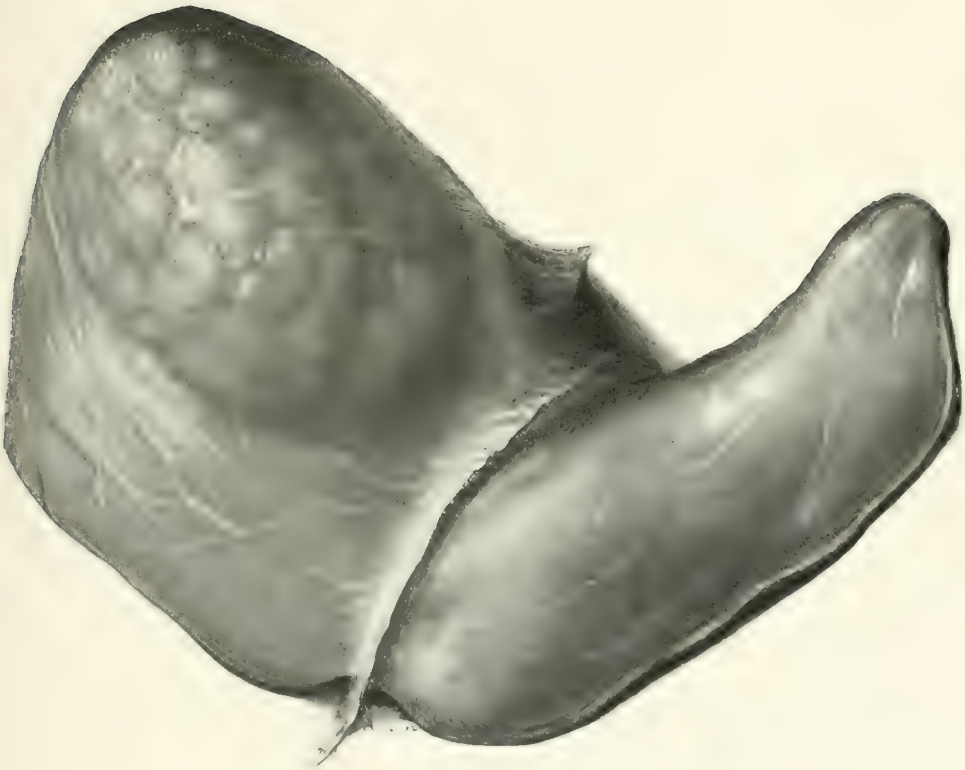
PLATE X. Macroscopic view of the cut surface of the liver, showing atrophic and hypertrophic portions.

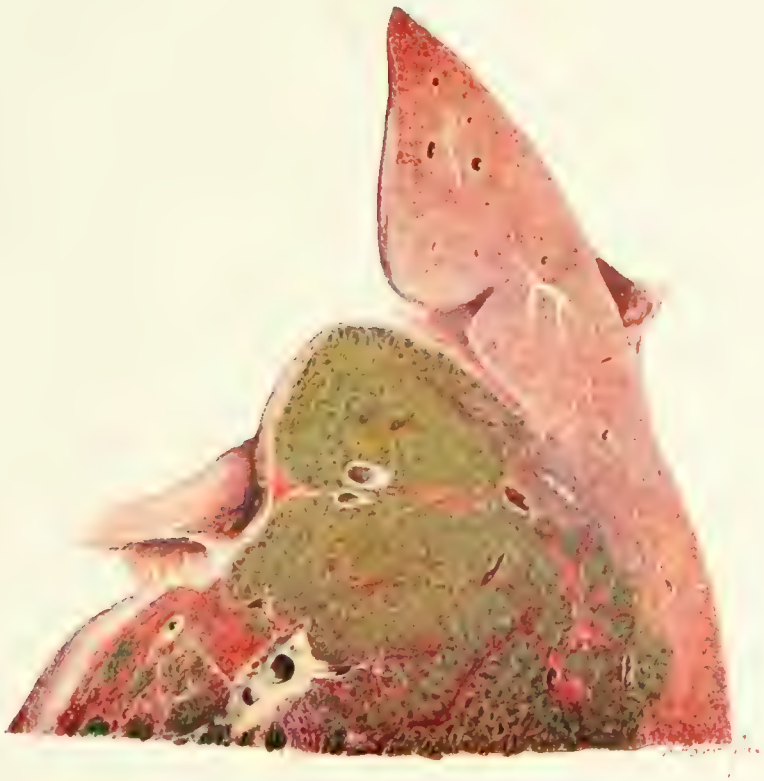
PLATE XI, FIG. 1. General liver substance. Sprouts are seen growing from the gall ducts in the portal spaces into the atrophic lobule. Near the central vein two degenerated liver cells can still be seen.

PLATE XI, FIG. 2. Margin of lobule in atrophic area. Regeneration of liver tissue from bile ducts. A karyokinetic figure is seen at the end of one of these sprouting ducts.

PLATE XII, FIG. 3. A portion of one of the nodules derived from hyperplasia of preserved liver substance showing the variation in the appearance of the cells.

PLATE XII, FIG. 4. Cells in such a nodule near the central vein. The cells are seen to be very large and to contain several nuclei besides small masses of bile.





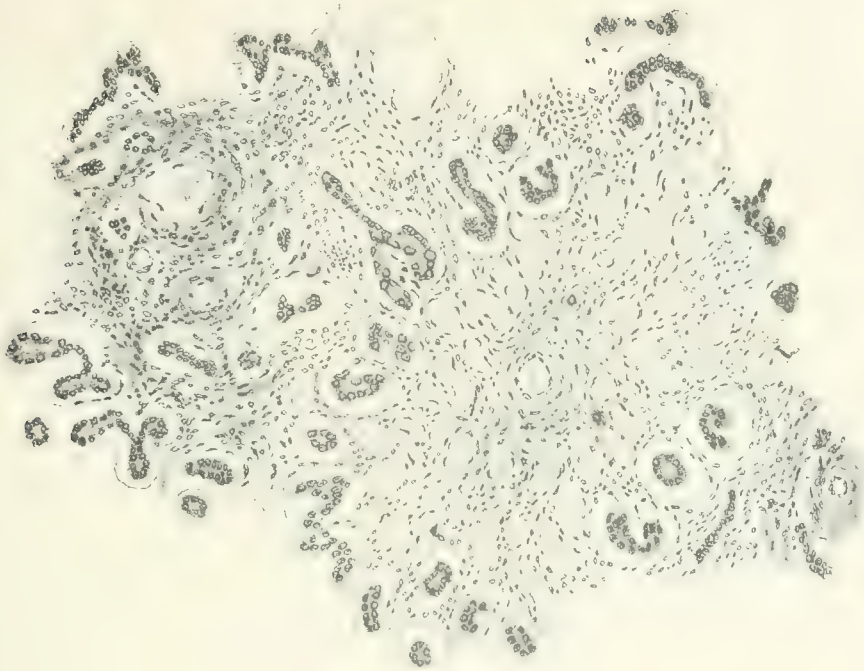


FIG. 1.

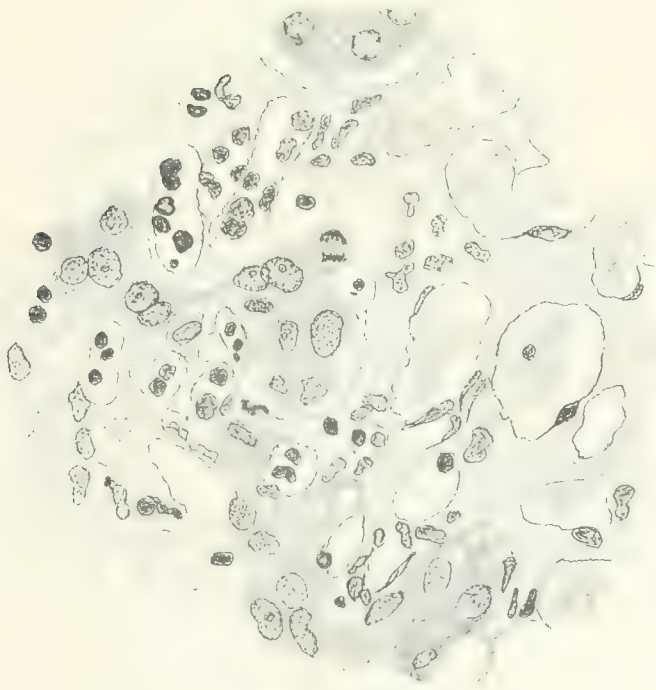


FIG. 2.

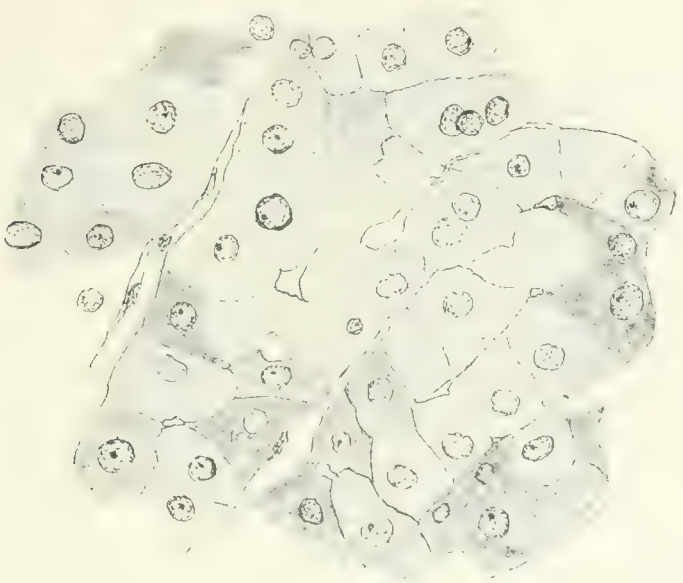


FIG. 3.

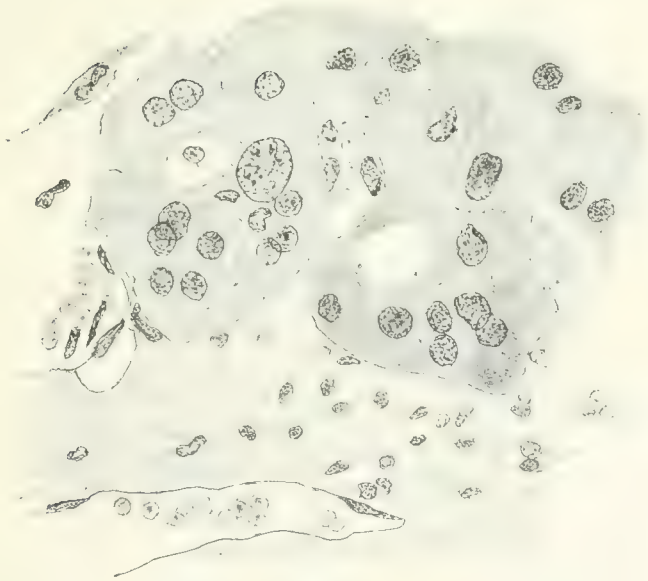


FIG. 4.

SURGICAL FEATURES OF TYPHOID FEVER.

BEING A SUMMARY OF THOSE CASES WITH SURGICAL FEATURES IN THE WARDS OF THE JOHNS HOPKINS HOSPITAL FROM JUNE, 1900, to JUNE, 1902, WITH ESPECIAL REFERENCE TO INTESTINAL PERFORATION.

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AND

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(From the clinics of Professor Osler and Professor Halsted.)

During the last two years there have been treated in the service of Dr. Osler at the Johns Hopkins Hospital 275 cases of typhoid fever. Recognizing the importance of familiarity with typhoidal conditions, and especially those connected with the abdomen, and the value of following the complications from their onset, we have made a practice of having the medical and surgical services work in the closest harmony. With this in view, our rule is to have a surgeon see all cases presenting any abdominal features. The importance of this is emphasized by Dr. Osler,[1] who says "It should be the especial duty of hospital physicians hereafter to study with more than usual care the earliest symptoms of perforative cases. . . . What is essential in every serious case is the watchful care of a man who will be quick to grasp changes in a patient's condition and who in such cases is in hourly collusion with his surgical colleague. . . . To leave the diagnosis of perforation to the attending physician is in too many cases to sacrifice the life of the patient."

In this paper the surgical features shown by the patients in the past two years will be considered.

The cases with surgical conditions can be divided into two groups: (1) conditions other than abdominal, (2) abdominal con-

ditions. Those in the first group are as a rule of minor importance and in the present series include (a) furunculosis and abscesses, including otitis media; (b) periostitis and perichondritis and (c), glandular affections. There have been no bone lesions or surgical complications or sequelæ other than those mentioned.

In the second group are included: (a) affections of the liver and gall-bladder, (b) appendicitis, (c) intestinal perforation, (d) suspected perforation—operation, (e) conditions causing abdominal symptoms, in which operation was not thought to be indicated.

Group I.—Conditions other than abdominal.

(a) *Furunculosis and abscesses, including otitis media.*

Furunculosis has occurred in 13 cases. The most frequent location was the buttocks. Some have been single, but the majority multiple, and in one case they were distributed over the whole body. They occurred as early as the eleventh and as late as the thirty-fourth day, the majority being in the third and fourth week. They had no influence on the course of the disease other than to prolong convalescence. Two subsided, one ruptured spontaneously, and the others were treated by simple incision. Cultures were obtained from two, yielding in both instances Staphylococcus pyogenes aureus.

In view of the danger of skin infection from the bath tub, patients suffering with boils are bathed in isolated tubs. Abscesses occurred twice, once in the axilla on the 8th day, and once on the buttocks on the 29th day. Both were treated by incision and cultures showed Staphylococcus pyogenes aureus. There was one case of otitis media (Med. No. 13473). On the 31st day there was pain in the right ear with redness and tenderness over the mastoid. The leucocytes were 3600. The temperature, which was running high, was not influenced. On the 34th day the tympanum was perforated and a small amount of thick yellow pus was obtained, from which Streptococcus pyogenes was grown. The discharge ceased in a few days. There was slight deafness.

(b) *Periostitis and perichondritis.*

Periostitis was observed twice, the clavicle being affected in both instances. The first (Med. 12376) occurred on the 36th day,

when distinct swelling was observed over the outer end of the left clavicle, which was very tender. An ice bag was kept constantly applied, the symptoms rapidly subsiding and disappearing completely by the 41st day.

The second (Med. 13118) occurred on the 41st day, during convalescence, with pain, swelling and tenderness over the left clavicle. The swelling was marked. There was severe pain on pressure and the skin was reddened. The temperature rose to 101.5°; the leucocytes were 12,000. Under the constant application of an ice bag, the symptoms had subsided by the 45th day although the temperature was still 100°. On the 47th day the temperature was normal and the tenderness gone, but there was still some thickening about the clavicle.

Perichondritis.—A single instance of this has been observed, occurring in a very severe case (Med. 12279) on the 23d day. The patient complained of pain on swallowing. There was considerable swelling and tenderness over the thyroid cartilage. The leucocytes were 9000. On the 25th day the swelling had increased and the skin was reddened. Death occurred on this day. No autopsy was obtained.

(c) *Glandular Affections.*

Enlarged cervical glands were observed in one case (Med. 13443) on the 67th day, associated with tonsillitis. They did not suppurate and subsided in about 12 days.

Mastitis occurred in three cases, which have been reported in full.[2] It appeared on the 30th day in two of these, in which one breast was involved. In the third case there was involvement of the right breast on the 13th day; of the left breast on the 18th and again on the 52d day but suppuration did not occur. There was rise in temperature and leucocytosis in two, in only one of which there was suppuration. The non-suppurative case subsided without surgical interference. Two cases suppurated and were incised. One of these yielded Staphylococcus pyogenes albus in cultures. In the other no culture was taken. They healed rapidly and the complication had no especial influence on the disease.

Group II.—Abdominal conditions.

(a) *Affections of the liver and gall-bladder.*

This division includes one case of abscess of the liver and five cases in which cholecystitis was suspected.

Case I.—*Typhoid fever; intestinal hæmorrhage; abscess of liver; operation; recovery.*

J. G. G. (Surg. No. 10943, Med. No. 11880) was admitted on the medical side Sept. 15, 1900, complaining of abdominal pain and bleeding from the bowels.

F. H. is negative.

P. H. is unimportant. During the last five months he has worked as a fireman on a boat running to Savannah, Georgia. He has never had dysentery nor typhoid fever. About six weeks ago he contracted a "heavy cold" and coughed a great deal. This has gradually improved but the patient has been unable to lie on his right side on account of pain in his chest and shoulder which is increased on coughing.

One week ago he began to have *abdominal pain* after a hard day's work. The pain was chiefly about the navel and in the upper right quadrant of the abdomen. It has been constant and has persisted until to-day when following the passage of bloody stools it has seemed to decrease somewhat. There has been no distention.

Vomiting began on the day after onset of abdominal pain and has been more or less frequent until four days ago. He has been unable to take food.

Bowels have been constipated until to-day, the last stool being two days ago. He has taken salts and castor oil, both followed by vomiting. To-day for the first time has flatus been passed in any amount.

Hæmorrhage from the bowels began this morning and there have been numerous bloody fluid stools during the day. The patient states that in amount these would fill an ordinary bucket. The blood was fluid and slightly darkened and the stools very offensive. Until to-day he has noticed nothing peculiar in the character of the stools. The patient has been in bed for a week. He has had more or less constant headache and fever; no epistaxis; no chills.

Examination.—The general appearance is that of a very sick man. The pallor is striking. He lies on his back, legs extended, sweating profusely, pupils somewhat dilated, tongue coated, suffering with paroxysms of severe pain.

Thorax.—Expansion is good, somewhat less on right side. A few râles are heard over both fronts. In the right axilla there is dulness. beginning at the 6th interspace. In the 4th and 5th interspaces there are numerous inspiratory râles, some of which are probable pleural. There is movable dulness. Heart sounds are clear.

Abdomen is flat, natural in appearance, everywhere tympanitic. Respiratory movements are decreased. In the upper right quadrant there is considerable tenderness on palpation and increased resistance of the rectus muscle. The left rectus is also slightly rigid. Between the right costal margin and the umbilicus there is a feeling as of something beneath the muscle, although no mass can be obtained. Liver dulness in the right mammillary line begins at the 6th rib and extends 5.5 cm. There is no definite dulness below the costal margin, though the note is less tympanitic for 4 cm.; no absolute liver dulness in the median line. The lower abdomen is soft and not tender. The spleen is not felt. There is no dulness in the flanks.

Rectal examination shows the bowel filled with blood clots, no tenderness. The pulse is 96, dicrotic, regular, and of low tension. Temperature, 101.6°. Respirations, 26. Leucocytes, 46,000.

Sept. 16, 1900.—The condition is little changed. There have been several bloody offensive stools, one of which amounted to 500 or 600 cc., consisting chiefly of clots; it contained no particles of tissue. The conjunctivæ have a yellowish tinge. The leucocytes are 58,000, hæmoglobin 52%, and the red blood corpuscles 3,680,000.

Sept. 17, 1900.—Yesterday the patient passed two bloody stools, this morning a large brown, slightly formed stool. The abdominal condition is practically unchanged. The spleen is readily felt.

The leucocytes were 69,000 (8 A. M.), and 75,000 (10 P. M.). The sputum is negative for tubercle bacilli.

Sept. 18, 1900.—Patient seems more comfortable—he sleeps well. In the right axilla there is dulness below the 6th rib, the breath sounds being absent over this area. Abdominal condition is much the same, with slightly increased distention and the walls rather more tense. There is no muscle spasm over the resistant area in the upper quadrant. The leucocytes were 67,300 (8 A. M.), and 73,000 (7 P. M.).

Sept. 19, 1900, Dr. McCrae.—The general condition is slightly better. The patient is still jaundiced. The thoracic movements are less on the right side. The flatness in the right axilla begins at the 6th rib and behind at the angle of the scapula. Over the area of dulness vocal fremitus and breath sounds are absent. The abdomen is a little full and the right costal groove almost obliterated. There is still resistance in the upper right quadrant of the abdomen. To exclude any thoracic condition, an exploratory puncture was made. A needle was inserted in the right thorax at the 6th interspace in the mid-axillary line and practically pure blood withdrawn. Coverslips showed no organisms. The leucocytes were 87,000.

The Widal reaction, which was suggestive on admission, is positive to-day.

Patient was transferred to the surgical side and prepared for immediate operation.

Note on operating table. Dr. Mitchell.—The abdomen is not distended. The respiratory movements are present. The right costal groove

is less marked than the left and some fulness of the right upper quadrant of the abdomen is noticed. Over this region there is absolute rigidity of the muscles and slight protective spasm on deep palpation. The point of greatest tenderness is about 5 cm. outside of and above the umbilicus. Here there is a feeling as of a rigid mass beneath the muscles. There is no dulness on percussion.

Operation.—Sept. 19, 1900; Mitchell; cocaine; chloroform; ether; Laparotomy through right rectus muscle. Walling off of intestines from region of liver. Collection of pus between liver and diaphragm and in the substance of the liver.

Incision in back at costal margin. Drainage of abscess cavity through anterior and posterior incisions. Partial closure with silver.

An incision was made through the right rectus muscle under cocaine, chloroform followed by ether being substituted as an anæsthetic as the peritoneum was reached. On opening the peritoneal cavity there was found to be a large mass at the outer side of the liver between the liver and the abdominal wall. The intestines were walled off with gauze pads and the mass explored. In separating the liver from the abdominal wall there was a gush of cloudy brownish fluid, about 500 cc. in amount, which was followed by yellowish thick pus of a slightly sweetish odor containing flakes of fibrin and a piece of necrotic tissue supposed to be liver. The cavity from which this fluid was evacuated was wiped out with gauze sponges. It was found to lie betwen the surface of the liver, the diaphragm, and the abdominal wall. The upper surface of the liver was excavated by an abscess cavity about 8 or 10 cm. in diameter with ragged edges. In order to give better drainage, an incision was made in the back about 10 cm. in length just below the costal margin. Through this a double drainage tube was inserted, surrounded by iodoform gauze, passing into the abscess cavity outside of the liver. The abscess cavity was packed anteriorly with iodoform gauze, extending into the cavity in the liver and walling off the general peritoneal cavity. The rectus muscle was partially closed by silver mattress sutures; the skin with subcutaneous silver.

Sept. 19, 1900, 10 P. M.—The patient stood the operation well. Immediately after the operation the leucocytes were 64,000. At 8.30 P. M. they had fallen to 46,000. There was considerable staining of the dressings with blood. The wound was examined and about the posterior drainage there was found to be between 500 cc. and 1000 cc. of clotted blood. There was still a thin, dark bloody discharge dripping rather freely from the drainage tubes. The upper wound was fairly dry. The patient's condition was extremely alarming. The pulse was very weak, and could not be accurately counted. The patient was restless, there was no nausea. The wound was dressed with a heavy gauze pad and a tight compress and binder placed over it, fixing the chest and abdomen as tightly as possible.

Sept. 20, 1900.—The leucocytes had dropped at midnight to 16,000; at 5 A. M. to 19,000; at noon to 12,000; hæmoglobin 45 per cent. The tight compress had evidently controlled the bleeding. The patient's temperature has been gradually falling and this evening at 8 it was 101.5°; pulse, 116. He has had frequent infusions during last night and today.

Sept. 22.—General condition at present is very good. The wounds are discharging freely a yellowish, thick brown secretion, having an ammoniacal odor. Bowels moved yesterday; no blood; small formed stool. Nourishment is well taken. Leucocytes (10.30 A. M.), 19,000; hæmoglobin, 36 per cent.

Sept. 23.—Last evening the patient began to complain of abdominal pain, which increased and became paroxysmal over the lower abdomen. There was also symmetrical distention of the abdomen. Bowels moved twice during the day. The patient is evidently in great distress, crying out with pain. A large, soft stool with much flatus followed the administration of a turpentine enema, affording temporary relief. He has vomited this morning. The abdomen is symmetrical, distended and tender; there is no muscle spasm and no rigidity. The patient cries occasionally with pain, principally on the left side of the abdomen. There is no visible peristalsis. There is slight bulging in the immediate neighborhood of the anterior incision.

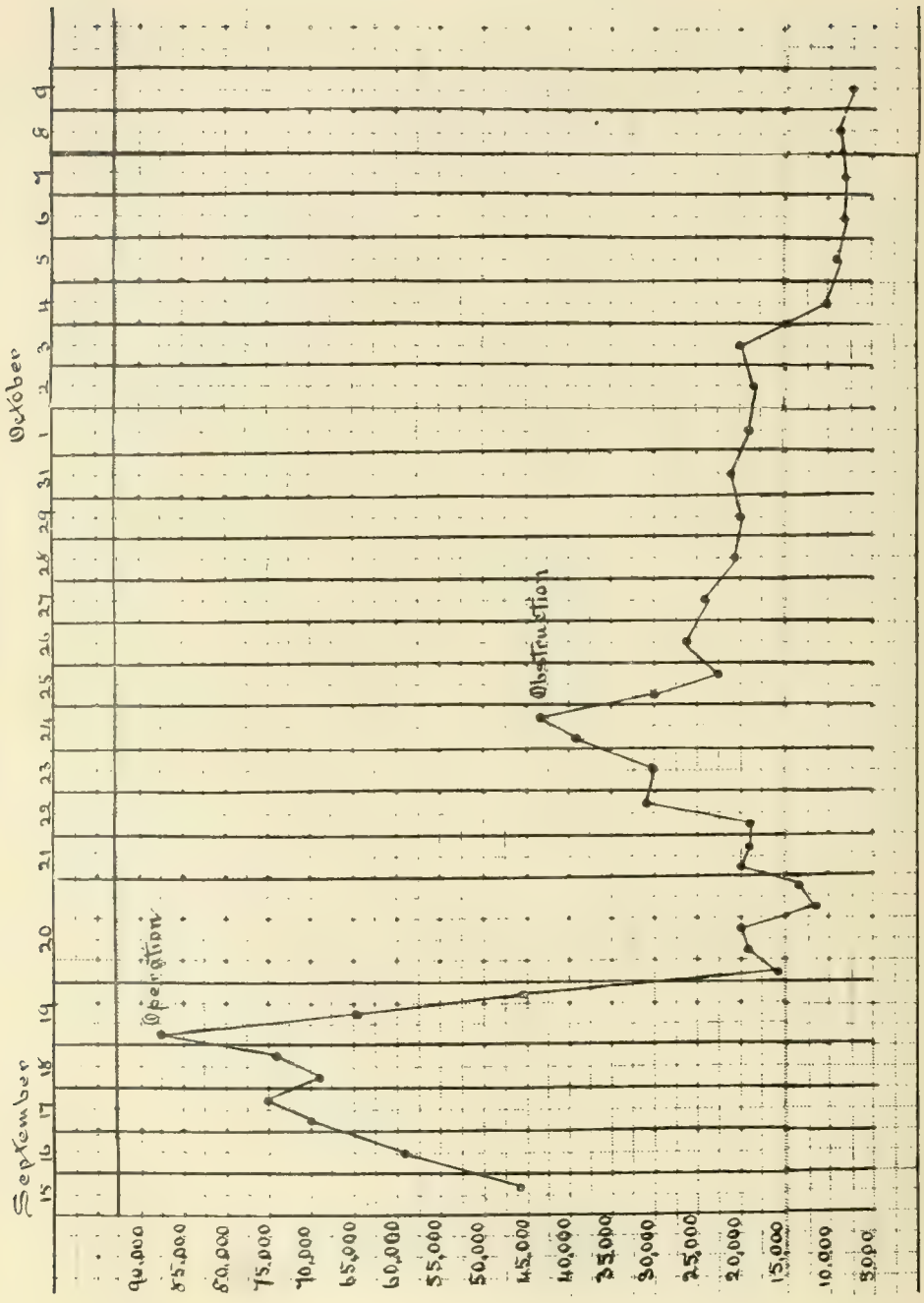
Sept. 24.—The abdominal pain and distention continued throughout last night. A great deal of flatus was passed with an enema. He vomited on several occasions. The temperature and pulse are both elevated. This morning the general condition is much better. The abdominal pain and tenderness have decreased and the patient feels more comfortable. The leucocytes rose with the abdominal pain on the evening of the 22nd to 31,000; on the evening of the 23rd, to 31,000; on the 24th, to 43,000. The hæmoglobin had fallen to 39 per cent. The patient has evidently had a slight obstruction, probably due to the gauze packing, which has been largely removed from the anterior wound and replaced by a smaller amount of fresh gauze. The obstruction has been relieved by the removal of the gauze and the administration of turpentine by mouth and in stupes and enemata.

Sept. 25.—The abdomen this evening is flat and soft; the distention has disappeared; the bowels have moved freely; the vomiting has ceased. There is a little discharge from the anterior wound and much sticky, rather gelatinous, yellowish, bile-stained discharge from the posterior wound. The leucocytes have fallen today with the relief of his obstructive symptoms to 22,500.

Sept. 27.—The patient's condition is excellent. All the original gauze has been removed from the wounds. The posterior wound is still discharging. Temperature is normal.

Oct. 16.—The wounds have been discharging very small amounts since last note and have gradually healed. The patient is discharged well.

CASE I. Leucocyte Chart.



Bacteriological notes.—Coverslips from the fluid and pus from the liver abscess at the time of operation, Sept. 19, showed no organisms. Careful examination for amœbæ was negative. Cultures taken at the same time were also negative.

Oct. 23.—Cultures and coverslips were made from the pus in the drainage tube. The coverslips showed bacilli and cocci. Cultures gaves Bacillus subtilis. Repeated examinations were made of the discharge from the tube throughout the whole course of the patient's illness. No amœbæ were ever found.

Remarks.—This patient on admission was very ill, his condition being rather alarming. The most striking features were the pallor and the recurring paroxysms of severe pain in the upper abdomen between which he was comparatively comfortable. On examination the persistent signs over the gall-bladder region with jaundice and the large leucocytosis were the most important points. On looking back over the case the diagnosis seems simple. At the time, however, having cholecystitis strongly in mind and the general opinion then tending toward symptomatic treatment of this affection, the medical side advised delay, especially as his general condition rather improved after admission, the constantly increasing leucocytosis being the only sign of progress in the process. The possibility of subphrenic abscess was considered but no conclusion as to its origin could be reached. Only one other case of abscess of the liver in typhoid fever appears in the hospital records. In this the abscess caused no signs which were recognized during life and was only found at autopsy. It was part of a general staphylococcus pyæmia.

Keen[3] states that in the literature previous to 1898 only 21 cases of hepatic abscess could be found, the first having been reported by Louis in 1841. In most cases it is primary, though it may be secondary to suppuration elsewhere. Most probably in a majority of cases pyogenic bacteria and the colon bacillus are the immediate cause, while in a few the typhoid bacillus alone may produce the abscess. Five of his cases had multiple abscesses and sixteen a single one. Of these 21 cases all but two died. Dr. Keen states that "Surgery can do but little actively in these cases. The treatment must be entirely symptomatic. The few that recover must be most fortunate and owe quite as much to nature as to the surgeon."

Da Costa[4] in 1898 reported 22 cases.

Curschmann[5] states "I know of no case in which the abscesses are due to a localization of the typhoid bacilli in the liver."

Perthes[6] in March, 1902, reports a case of abscess of the liver which developed during convalescence. The patient had been out of bed for a week when on the 49th day the temperature began to rise. On the 69th day he complained of pain in the epigastrium. He was operated upon on the 81st day and a large subphrenic abscess was drained. The patient recovered. Coverslips from the pus showed streptococci and bacilli. The Bacillus typhosus was isolated from cultures. He reviews the reports of the cases, in three of which, including his own, the bacillus typhosus was obtained in cultures from the pus in combination with pyogenic cocci. All three of these cases were published after the work of Keen and Curschmann.

Cholecystitis has been suspected in five cases of this series during the course of typhoid fever. Three were not operated on and recovered; in one perforation of the gall-bladder occurred, followed by general peritonitis and death, without operation, and the fifth was operated upon and recovered.

Case II.—*Typhoid fever; relapse; symptoms of cholecystitis on eighth day of relapse; recovery without operation.*

H. S. P. (Med. No. 11865), male, white, aged 29. Admitted on the medical side Aug. 7, 1900, on the 6th day of typhoid fever. The Widal reaction was positive on the 20th day. The attack was mild and his temperature was normal on the 15th day. On the 21st day a relapse began. On August 28, the 27th day of his disease and the 8th day of his relapse, the patient complained of pain in the right hypochondriac region. There was tenderness on palpation, but no great rigidity and no muscle spasm.

Aug. 29, Dr. McCrae.—The pain below the right costal margin continues. The abdomen is flat. There is no visible prominence. The tenderness is increased on the slightest palpation. There is well marked muscle spasm but nothing definite is felt. The liver edge is just palpable outside of the rectus. There is no rise of temperature, which has been about 101°; no jaundice. Leucocytes, 18,000.

Aug. 30.—General condition is good. Patient still complaining of a great deal of pain in the region of the gall bladder. The edge of the liver is still below the costal margin.

Aug. 31.—The pain has completely gone. General condition is excellent. From this time the patient's convalescence was uninterrupted, He was discharged well with no abdominal symptoms on Sept. 20, the 50th day of his illness, and the 31st day of his relapse.

Remarks.—This case at the time impressed us as one of cholecystitis. The pain was so severe in the right hypochondrium, localized over a small area and associated with such marked muscle spasm and leucocytosis that the suspicion seemed at any rate well founded. It is of interest that this occurred during the relapse.

CASE III.—*Typhoid fever: convalescence: symptoms of cholecystitis on the 19th day and again on 50th day: recovery without operation.*

E. S. (Med. No. 12892), white, female, aged 24. Admitted on the medical side on May 11, 1901, on the 14th day of typhoid fever. The Widal reaction was positive on the 21st day. The temperature on admission was 102°. Abdominal symptoms were not marked; leucocytes, 6400. The attack was rather mild until the 19th day when the temperature began to rise again and on the 23d day reached 104.5°, and continued high until the 28th day when it again began to fall and ranged between normal and 102° until the 48th day, after which the temperature was normal for three days. The abdomen was practically negative. The patient complained a great deal of pain in the back and slight pain in the shoulder joints.

June 16, the 50th day, she began to have pain in her epigastrium, vomited a small amount of food, and the attack passed off.

June 17, Dr. McCrae.—The patient complained of sudden severe pain in her epigastrium, and vomited. She was found sitting up in bed, which position she said gave some relief; evidently in severe pain. There is nothing to be found in the region of the gall bladder, although there is some pain on pressure there. There is no jaundice.

9 P. M., Dr. Futcher.—The patient is still suffering with abdominal pain, which shoots into the back. She has vomited 200 cc. of yellowish brown fluid. There is marked tenderness in the right hypochondrium; some rigidity of the rectus. Leucocytes, 8500.

June 18, 5 A. M.—The patient slept quietly until 4 A. M. when she awoke with a violent shaking chill, nausea, temperature 101.6°, pulse, 120. She has vomited frequently. Leucocytes, 10,000. The patient looks ill. On palpation there is tenderness and slight muscle rigidity in the right hypochondrium. Leucocytes (9 A. M.) 8200; (1 P. M.) 7100.

June 18, Dr. Mitchell.—There is no jaundice. Slight general tenderness is elicited on deep palpation, most marked in the right hypochondrium; no muscle spasm; no rigidity of right rectus. The abdomen is soft, not distended. Operation is not advised.

The temperature rose at noon to 104° and gradually fell throughout the day, reaching normal the next morning.

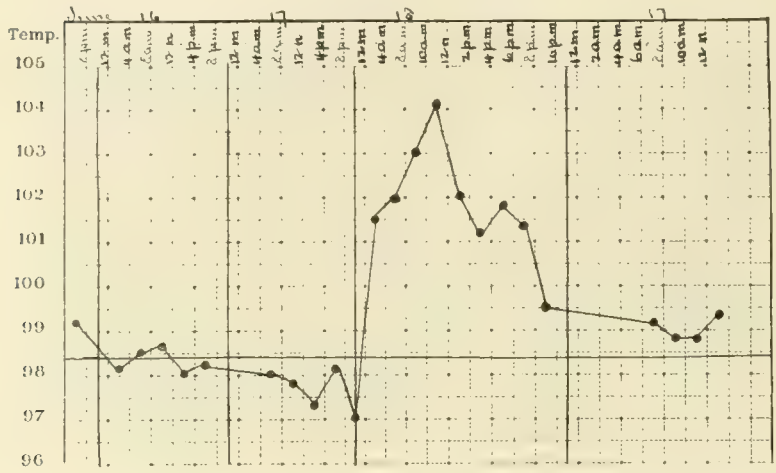
June 19, Dr.McCrae.—General condition is good. Temperature is normal. There is well marked jaundice and yellow tinge of the conjunctivæ. Leucocytes, 8500.

June 21 and 22.—There is recurrence of the nausea and vomiting, the

temperature rising above 101°. The gall bladder is not palpable. There is a return of the tenderness in the region of the gall bladder and the yellow tinging of the conjunctivæ is still noted. Leucocytes, 11,500.

The symptoms rapidly subsided and the patient left the hospital well on the 3d of July, the 66th day of the disease.

CASE III. TEMPERATURE CHART.



Remarks.—There seemed little question as to the diagnosis in this case. In view of the unfortunate result from non-interference in Case V, we would be inclined now to advise operation as offering greater safety.

CASE IV.—*Typhoid fever; mild attack; convalescence; symptoms of cholecystitis on 23d day and again on 48th day; recovery without operation.*

M. K. (Med. No. 13418), white, female, aged 25. Admitted on the medical side Sept. 8, 1901, on the 7th day of typhoid fever. The attack ran a mild course. The Widal reaction was given on the 24th day. Convalescence was slow and tedious.

Sept. 25, the 23d day of the disease: The patient has complained of some pain since yesterday, which extends into the back. The temperature, which for the past few days was normal, is now 102°. On palpation the abdomen is soft. There is no rigidity nor muscle spasm. There is tenderness on the right side. Leucocytes, 6300. The temperature rose at night to 104.6° She complained of soreness in the whole abdomen, pain in the back, and headache. The pain is just beneath the costal margin on the right side. On palpation the gall bladder region is extremely tender. There is some resistance on pressure. No

mass is made out. There is no muscle spasm; no rigidity. Leucocytes, 7500.

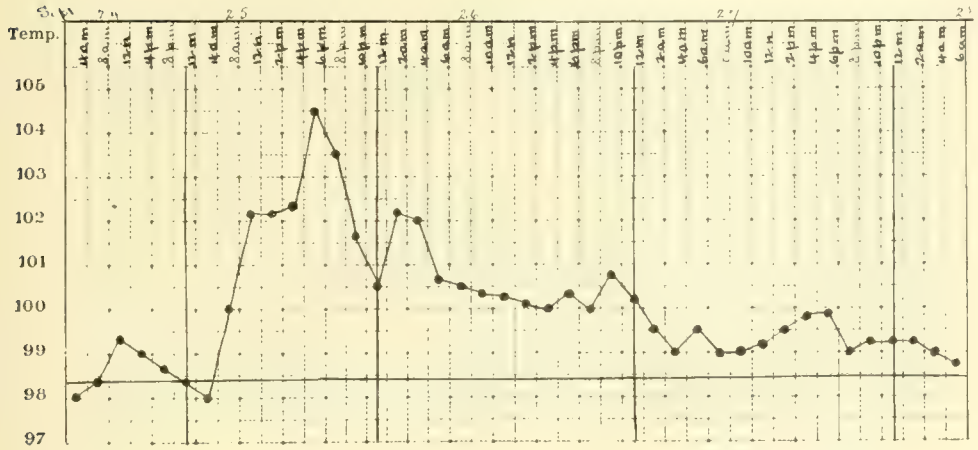
Sept. 27, Dr. McCrae.—There has been an elevation of temperature for the past two days with much pain just below the right costal margin, but no jaundice. The abdomen is flat. There is tenderness over the region of the gall bladder, and on deep pressure some muscle spasm, but nothing definite is felt.

Sept. 30.—The temperature has gradually reached normal. General condition is good.

Oct. 20, 48th day.—There is a second attack of pain in the region of the gall bladder. The abdomen is very tender. There is no jaundice. Nothing is to be felt in the region of the gall bladder. Leucocytes, 7200. There is no rise of temperature.

Pain, tenderness and rigidity persisted for three days and gradually subsided. There was no recurrence. She left the hospital well on Oct. 27, the 54th day of the illness.

CASE IV. TEMPERATURE CHART.



Remarks.—This case closely resembles Case III except that here there is no jaundice. Convalescence was established. The patient was doing well when the sudden rise of temperature accompanying the abdominal symptoms was ample evidence of an acute intra-abdominal process. Here, as in Case III, the trouble developed while the temperature was normal in convalescence.

CASE V.—*Typhoid fever; severe attack; abdominal symptoms marked throughout; symptoms of cholecystitis on 9th day; intestinal hæmorrhage; no operation; cholelithiasis; perforation of gall bladder; general peritonitis; death; autopsy.*

A. E. H. (Med. No. 13335), white, female, aged 38. Admitted on the medical side on Aug. 21, 1901, on the 5th day of typhoid fever. The temperature on admission was 104°; pulse 112; very severe attack. The Widal reaction was positive on the 6th day. Abdominal symptoms were marked throughout the attack. Patient extremely dull. Leucocytes, 6600.

Aug. 23, 1901, Dr. Cole.—The abdomen is distended and full, but the walls are soft with liver dulness just reaching the costal margin. There is tenderness in the right lumbar and iliac regions.

Aug. 24.—Leucocytes, 9200.

Aug. 25, Dr. Futcher.—The patient stiffens up the right rectus and complains of considerable tenderness when palpated. No mass is to be felt. The tenderness extends as low as the umbilicus on the right side. There is slight movable dulness in both flanks. On the 8th day, Aug. 25, sponges were substituted for tubs, after which the temperature was higher than before, running above 105° and yielding little to the sponges. Leucocytes, 12,700.

Aug. 26, Dr. Futcher.—The patient is still complaining this morning of pain in the right hypochondrium. The abdomen is somewhat distended. The respiratory movements are free throughout. On palpation there is very marked sensitiveness even on light pressure in the right hypochondrium. The right rectus is more rigid than the left. Leucocytes, 20,000. During the afternoon she had a severe shaking chill. The temperature rose to 106.3°; pulse 112 to 148. She complained of no more pain than during the morning, but the tenderness over the region of the gall bladder was very pronounced.

Aug. 27.—Leucocytes, 8500.

Aug. 28, 11th day.—Temperature is about the same. The tenderness in the right hypochondrium and about umbilical region began to subside yesterday. This morning considerable pressure could be exerted without causing severe pain. There is still moderate tenderness with definite deep-seated resistance. The gall bladder cannot be made out.

Aug. 28, 1901, 10.30 P. M., Dr. Futcher.—The patient has become very drowsy and dull during the day; does not respond to questions. The abdomen is a trifle distended in the umbilical and hypogastric regions. There is no increase in fulness in the right hypochondrium where there is a little more tenderness than at the previous examination. The gall bladder is not felt. There is no muscle spasm. Respiratory movements are free.

Aug. 30.—Slight hæmorrhage from the bowels; leucocytes, 13,000.

Aug. 31, Dr. Futcher.—The patient has been more dull for the past two days and does not respond to questions. The rigidity of the abdomen is more marked on the right side. She is extremely dull; markedly cyanotic; perspiring slightly; cannot be aroused. Temperature 105.4°; pulse cannot be counted at wrist. Leucocytes, 10,500. The abdomen is not distended. Respiratory movements are free. Nothing

can be definitely felt in the hypochondrium. Pressure causes a great deal of pain. Abdominal muscles are rigid and there is some muscle spasm. Died at 6.30 P. M., 14th day.

Autopsy showed general peritonitis; perforation of gall bladder, which was contracted around a single large stone. Typhoid fever. Hyperplasia of mesenteric glands. Ulcerated Peyer's patches in the lower ileum. Acute splenic tumor. Parenchymatous degeneration of the liver and kidneys. Cystitis.

Remarks.—This patient was seen constantly in surgical consultation. Undoubtedly operation should have been advised when first seen. The diagnosis of cholecystitis was evident, but because the gall-bladder was never distended, operation was decided against. The possibility of the perforation of an undistended gall-bladder was never considered. The case is important as suggesting the advisability of an exploration of the abdomen where the diagnosis of cholecystitis is evident. It is difficult to state when the actual perforation occurred. A strong factor in its production was undoubtedly the presence of a single large stone.

CASE VI.—*Typhoid fever; severe attack; abdominal symptoms on 6th day; symptoms of cholecystitis on 22d day; operation; cholecystostomy; recovery.*

W. C. (Medical No. 13159), male, white, aged 11. Admitted on the medical side July 19, 1901, on the 5th day of typhoid fever,—a sharp attack. His temperature on the day of admission was 104.8°. The Widal reaction was positive on admision. Bacillus typhosus was obtained from blood culture on the day after admission. The abdomen at entrance was soft, no tenderness. General condition is good. Leucocytes, 4300.

July 20, 6th day, 1 P. M.—The boy was found crying with pain about the umbilicus. Leucocytes 5800. The pain rapidly passed away and he was quiet during the rest of the afternoon.

5.30 P. M.—The boy is complaining of pain and headache. He is lying on his back, the left knee drawn up, but it can be straightened out without causing pain. His face is flushed.

Abdomen is natural; respiratory movements free. The pain is indefinitely localized. On palpation the abdominal walls are rigid; no muscle spasm; no vomiting. Leucocytes, 5100.

During the next two weeks there were no abdominal symptoms. The boy was quiet, his temperature ranging about 103° to 104°, gradually subsiding, touching normal after a tub on July 31, the 17th day, rising again to 102°, and continuing in this way until Aug. 4, responding well to tubs, at times dropping four degrees.

Aug. 5, 22d day, Dr. Cole.—This morning at 9.15 he is complaining of quite severe pain in the abdomen, which he says he felt last night

for the first time. He cries whenever an attempt is made to palpate the abdomen, and cries with pain when he takes a deep breath. Just to the right of the umbilicus there is a prominence about 5 cm. in diameter.

Surgical consultation (Dr. Mitchell).—The abdomen moves freely with respiration. The walls are very thin and numerous coils of intestine can be made out. Just to the right of the umbilicus is a *visible tumor* about 5 cm. in diameter, round in outline, which rises and falls with respiration, and does not seem to change its shape. The patient cries occasionally with cramping pain in this region. On percussion the left side of the abdomen is tympanitic; likewise the lower portion of the right abdomen. As soon as the tumor is reached there is marked impairment of the note, though it is not absolutely flat. The impairment extends into the flank. There is no absolute dulness. The liver dulness extends below the costal margin. On palpation the left side of the abdomen is perfectly soft, not tender, and deep palpation is everywhere possible. As soon as the right rectus is reached the difference is apparent. Along the crest of the ileum the abdomen is quite soft. The right rectus is more tense than the left. Over the mass the tenderness is exquisite. The boy cries out even when light percussion is attempted. The abdominal wall is perfectly rigid. There is active muscle spasm. Tenderness and spasm are present over the whole upper right quadrant, the upper portion of the right rectus being perfectly rigid and board-like. This rigidity extends along the costal margin and, with the tenderness, into the right flank. There is no jaundice. The edge of the liver is not felt. Leucocytes 10,000. The temperature has risen from 99° last night to 104.8° this morning. Operation is advised. The boy himself proposed operation and wished to have "this ball which hurts him cut out of his stomach."

Operation.—Mitchell; cocaine, 1-3000. Laparotomy; cholecystostomy; incision through right rectus; drainage of gall bladder with tube.

The patient was given ⅛ gr. of morphia, hypodermically, one hour before operation, and a second ⅛ gr. just at the beginning of the operation. The operation was done entirely with 1-3000 cocaine. An incision was made through the right rectus muscle about the level of the umbilicus, and the peritoneal cavity opened. There immediately escaped some turbid fluid and a bluish, enormously distended gall bladder presented with omentum slightly adherent over its surface. The lower portion was entirely free. At one place on its surface was a whitish area, possibly a point for future perforation. The gall bladder was packed off with gauze, secured by four traction sutures, and aspirated. Its walls were extremely thin and it was impossible to place the traction sutures without passing through into the cavity of the gall bladder. The first fluid drawn from the gall bladder was thin and cloudy. On microscopical examination it contained numerous bacilli, mostly clumped. The fluid became bile-stained as the bottom

of the gall bladder was reached. In all about 300 cc. of fluid were withdrawn from the gall bladder. There were no gall stones. A small rubber tube was inserted, secured by a purse string suture of catgut. The gall-bladder was packed around on all sides with bismuth gauze. The muscles were partially closed by silver sutures. The boy stood the operation without complaint and laughed and talked with the bystanders. His pulse showed no change and he went to the ward in good condition.

His temperature fell rapidly and reached normal on the day following the operation. His convalescence was uninterrupted. There was a free discharge of bile. The gauze packing was gradually withdrawn. The boy left the hospital on Sept. 25 in excellent condition with a small biliary fistula, which has since closed.

Bacteriological notes.—Cultures and coverslips from the fluid in the peritoneal cavity were negative. Coverslips from the gall bladder showed numerous bacilli, mostly clumped. The cultures yielded a pure growth of Bacillus typhosus.

Remarks.—In this case there was no question as to the diagnosis, the symptoms from the first pointing to an inflamed gall-bladder. The rise of temperature to 104.8°, the presence of tenderness and muscle spasm in the right hypochondrium, with lastly the presence of a *visible rounded tumor*, associated with a rising leucocytosis, all evidenced an active process. The boy himself realized the advisability of operation and begged to have it performed.

Review of the Symptoms.—In considering these five cases it is seen that the time of the onset of the cholecystitis varied widely. The earliest was on the 9th day and the latest on the 50th day during convalescence. In two it occurred after the temperature had become normal and in both it caused a sharp, sudden rise to over 104°. In one it came on during a relapse. The onset was sudden and with pain in all. In one there was pain and vomiting and in another a chill. Of the symptoms, pain occurred in all, usually fairly constant, but in Case VI paroxysmal. The pain was severe and a striking feature in all. Tenderness or pain on palpation below the right costal margin, and with it muscular rigidity or muscle spasm, occurred in all. Vomiting was present in only one instance. There was a chill in one after the onset. Definite rise in temperature, associated with increased pulse rate, occurred in four of the cases, in only one of which, however, was the rate of respiration also higher. Jaundice was present in one

case only. Leucocytosis, varying from 10,000 to 20,000, was present in four instances; in the fifth the highest count was 7500. The gall-bladder was positively felt in only one case. The duration of symptoms, where no operation was done, varied from four to eight days.

The picture of symptoms as shown by these cases is a sudden onset with pain in the right hypochondrium with which chill or vomiting may be associated. The pain continues with tenderness and rigidity or muscle spasm on palpation. Moderate leucocytosis is usually found. The temperature and pulse rate usually rise. The gall-bladder may be felt. Jaundice of a slight grade may follow.

Treatment.—With expectant treatment three patients recovered and one died, who at any rate would have had a much better chance with early operation. The only operative case recovered. Tapping can not be considered now a justifiable procedure, and the indications that justify tapping surely justify exploration. To advise tapping a suspected appendix abscess is about as rational as to advise tapping the gall-bladder with cholecystitis. As to the indications for operation, one must decide in each case. Certainly with well marked and severe symptoms as in Case III an exploration means less risk to the patient than waiting. Of course, seeing a patient from hour to hour, one hopes to appreciate increasing gravity in the condition and advance in the symptoms, but error is easy; a perforation may occur without much increase in the symptoms and the time for interference be past, or at any rate the chances for recovery diminished. Exploration means but little risk. Expectant conservatism may mean the same or it may mean the loss of the patient as we found in Case V.

Cholecystostomy is one of the most satisfactory of cocaine operations as is shown most strikingly in Case VI, the patient being a boy only eleven years of age and children as a rule being the poorest of cocaine subjects. The boy scarcely complained at all, while his pulse and general condition were absolutely unaffected. As is brought out by Lennander (7), there is great difference in the sensibility of the parietal and visceral peritoneum. The gall bladder itself can be handled and sutures passed through its wall without any pain. The parietal peritoneum, on the other hand, must be treated most carefully and in introducing the gauze packing we

have found it of the greatest assistance to depress the gall-bladder and pass the gauze into place along the surface of the gall-bladder, allowing it to touch the parietal peritoneum only when pushed up by the gall-bladder returning to its natural position. We may add that the gall bladder should always be explored for stones, although the presence of bile will show that there is no permanent obstruction of the cystic duct, and will exclude the probability of a lasting biliary fistula.

(b) *Appendicitis.*

This group may be divided into two classes, firstly, those which are admitted with symptoms strongly suggesting appendicitis, and secondly, appendicitis developing in the course of typhoid fever. In the first class are three cases (brief extracts of which are given). In the second there is a single case.

CASE VII.—*Typhoid fever; admitted with diagnosis of appendicitis; no operation; recovery.*

D. M. T. (Surg. No. 11446, Med. No. 12468), white, male, aged 31. Admitted on the surgical side Jan. 21, 1901, complaining of obstruction of the bowels.

P. H.—Eight years ago the patient had jaundice lasting a week. Four years ago he had a tape-worm, which was removed in December last, since which time he has suffered from constipation and has lost some weight.

P. I.—One month ago he had a severe "spell" of indigestion, constipation, and some temperature. He worked for two or three days, but on the fifth day went to bed, with a temperature of 104° and slight jaundice. His bowels moved with difficulty. He improved for a week and then became constipated with considerable straining at stools. There was no vomiting. There were general pains throughout the abdomen and some tenderness in the region of the umbilicus. He was brought to the hospital as a case of appendicitis.

On admission the temperature was 101° rapidly rising to 103°; pulse 90; leucocytes, 7000. The patient did not look especially ill. The abdomen was soft and not distended. There was some tenderness on deep palpation about the umbilicus, rather too high for an appendix. The spleen was not palpable. Typhoid fever was suspected.

Two days after admission the Widal reaction was positive. He was transferred to the medical side where he ran a mild course of typhoid fever without complications. His abdominal symptoms had disappeared at the time of the transfer. He was discharged from the hospital well on Feb. 16.

Case VIII.—*Typhoid fever; admitted with symptoms of appendicitis; no operation; recovery.*

T. G. (Medical No. 13221, Surg. No. 12146), male, age 21, black. Admitted on the surgical side complaining of headache and pain in the abdomen.

P. I. began seven days ago with headache, fever, and pain in the abdomen, especialy marked on the right side. On admission the temperature was 103°; pulse 96; leucocytes 7000. The abdomen was not distended, symmetrical; respiratory movements everywhere present. There was some rigidity and tenderness over the whole abdomen, most marked on the right side. There was resistance to palpation in the right iliac fossa and gurgling on deep pressure, but no muscle spasm and no mass to be made out. The spleen was not palpable.

The patient's temperature remained high during the next two days, rising above 104°, and not falling below 100°. The tenderness in the right iliac fossa and the abdominal rigidity gradually disappeared. He was transferred to the medical side as a case of typhoid fever. The patient ran a typical course of typhoid fever. The Widal reaction was positive on the 9th day. He left the hospital well after an illness of seven weeks.

Case IX.—*Typhoid fever; marked symptoms of appendicitis on admission; no operation; recovery.*

S. A. J. (Medical No. 13523), female, black, aged 34. Admitted to the medical service Oct. 1, 1901, complaining of headache, and pain in the abdomen. One week ago while ironing, she suddenly felt a pain in her head which was so severe as to cause her to stop working and sit down, when she fainted. She became conscious in a few minutes. Two days later on account of pain in the abdomen and increasing headache she went to bed, had fever and chilly sensations with nausea and on one occasion vomiting. Her bowels moved three days afterwards. The pain in the abdomen was general at first but soon became localized in the right iliac fossa.

On admission the patient was in good condition; chest negative; abdomen not distended; respiratory movements limited and practically absent below the navel. The patient complained of pain in the right iliac fossa on palpation, there being a distinct difference between the two sides, the left soft without rigidity and muscle spasm. On the right side there was considerable tenderness about McBurney's point and the suggestion of a resistant body. The spleen was not palpable. Leucocytes, 3000; temperature, 102°. Vaginal examination was negative.

Oct. 4.—The patient is much more comfortable, does not complain of abdominal pain, and is less tender on palpation in the right iliac fossa. The mass previously felt has almost entirely gone. The temperature on admission was 102°. Since admission it has ranged between 102° and 103°. The Widal reaction was positive on admission and was very

slightly suggestive at the end of the fourth week. The patient ran a typical mild course of typhoid fever, had no recurrence of pain in the region of the appendix, and was discharged well on the 31st of October.

These cases are noted especially to lay emphasis on the necessity of keeping in mind the possibility of mistaking the abdominal symptoms of typhoid fever for those of an acute appendicitis. The onset may be moderately acute and not a suspicion of typhoid fever even entertained. The mistake is not uncommon and one hears of patients with typhoid fever being operated on for this reason. In the present cases it may be said that in none was the diagnosis long in doubt. The low leucocyte count in typhoid fever is usually a very helpful point. In none of these three cases was the count above 7000. Only once have we observed an acute appendicitis developing during the course of typhoid fever. There was no evidence that this was due to a typhoid process, either through ulceration or infection of the appendix with the typhoid bacillus, the only organisms obtained being Bacillus subtilis and saprophytes.

Case X.—*Typhoid fever; abdominal symptoms on 12th day; operation; pre-perforative ulcers and acute appendicitis; death; autopsy.*

A. C. (Surg. No. 10940; Med. No. 11869), male, black, aged 21. Admitted on the medical side Sept. 11, 1900 about the 6th day of typhoid fever. His temperature on admission was 103.7° and remained high throughout his illness, reaching 105.6° and dropping two or three degrees after his sponges. The Widal reaction was positive on the 7th day.

Abdominal symptoms were not marked on admission. On the 9th day there was some tenderness about the navel. About the 10th day, Sept. 15, there was tenderness about McBurney's point, the patient wincing on slight pressure, but there was no muscle spasm.

Sept. 17, Dr. McCrae.— The patient was seen in the afternoon and again about 11 P. M., on which occasion the general condition was good, but he complained of severe abdominal pain just at the right of the navel. Respiratory movements were present but not very marked. On palpation there was no tenderness over the left half of the abdomen, but very marked over the right, especially about the navel. There was no muscle spasm. At 11 P. M. he cried out at the slightest touch in the right iliac fossa. Leucocytes at 8 A. M., 7700; at 10 P. M., 8500.

Sept. 18.—He complained of severe pain at 5.45 A. M. At 6.15 he was easier but complained of pain at the slightest touch. At 8.30 A. M.

he was found in dorsal decubitus; knees drawn up; respirations, 30; pulse, 120. The abdomen was soft and not distended; respiratory movements slight; pain constantly complained of. On palpation there was some general tenderness, most marked in the right side. There is definite muscle spasm in the right iliac fossa; no dulness. Leucocytes, 15,000 at 7 A. M., 20,000 at 9 A. M. He was seen in consultation at 9.30 A. M. by Dr. Mitchell, and an immediate exploration decided upon. The presence of pain on admission was the disturbing factor, but the definite increase of pain with a larger area of tenderness seemed with the leucocytosis, to justify an exploration on the ground of a probable abdominal complication.

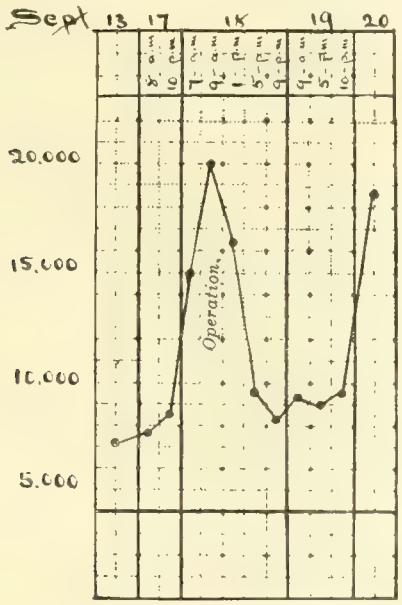
Note on operating table, Sept. 18, 1900.—Dr. Mitchell. The respiratory movements are present over the upper abdomen and decreased over the lower. The abdomen is symmetrical, no fulness in the flanks. There is some general rigidity on palpation, both recti being tense. There is no tenderness on the left side. The greatest point of tenderness is just to the right of the umbilicus, pressure here causing the patient to cry out. There is marked tenderness over the whole lower right abdomen. In addition to the rigidity there is an area of protective spasm just to the right of the umbilicus at the point of greatest tenderness.

Operation.—11 A. M.; Mitchell; cocaine; chloroform. Exploratory laparotomy. Demonstration of pre-perforative ulcers in ileum, with large mesenteric glands. Cloudy, brownish fluid about cæcum and appendix and in the pelvis. Appendectomy for acute appendicitis. Drainage.

An incision was made through the right rectus muscle under cocaine anæsthesia and the peritoneal cavity opened. There was no free fluid directly beneath the incision. The parietal peritoneum beneath the incision, which was at point of greatest tenderness, was inflamed and its blood-vessels injected, and corresponding to this point were two ulcerated Peyer's patches in the ileum. These patches were elevated beyond the serous surface of the intestine. They were dark purplish in color. The serosa over them was dull. The blood-vessels and lymphatics about them were very prominent and tortuous, the whole condition suggesting a pre-perforative stage. Handling of the ulcerated area caused the patient to complain of the same pain which he had experienced on pressure on this region before operation. The ileum was carefully examined. No perforation was found. The appendix was then sought. In lifting up the cæcum to expose the appendix, which was lying below and a little behind the cæcum, there was a gush of about 500 cc. of thin, brownish, odorless fluid, which was situated behind the cæcum about the appendix and extended down into the pelvis. This was wiped out with gauze sponges and at this stage of the operation on account of the pain a few whiffs of chloroform were administered. The appendix was distended, tense, and very rigid, its

surface vessels large and tortuous, presenting the appearance of acute inflammation. The appendix was removed. The region of the appendix was wiped out with salt sponges. Iodoform gauze drainage was placed to the suspicious ulcers and an iodoform and protective drain extending into the pelvis. The operation lasted an hour and twenty minutes. The pulse at the beginning of the operation was 120; at the end 130.

CASE X. LEUCOCYTE CHART.



Sept. 18, 9.30 P. M.—The patient's general condition is excellent. He has recovered well from the operation. The leucocytes show a steady fall from 20,000 at 9 A. M. before the operation to 8200 at 9 P. M. There is a corresponding fall in pulse and respiration; temperature, 104°. The patient is quiet, complaining very little; has voided urine and passed a soft stool. The abdomen is flat; respiratory movements free. There is no tenderness in the left side of the abdomen, the only tenderness being about the incision. There is no rigidity nor muscle spasm. The gauze dressing is soaked with blood stained fluid.

Sept. 20.—The patient was doing very well until 9.30 last night when his pulse became weak and rapid; the skin cold and clammy. He improved somewhat under stimulation.

At 10.30 P. M. he had a peculiar attack, in which the respirations reached 70 or 80, and a similar attack two hours later lasting for a few minutes. Infusion with salt solution was followed by some

improvement. After 3 A. M. the pulse could not be counted. Leucocytes, 18,000; temperature, 102°. He died at 6 A. M.

Bacteriological notes.—Coverslips from the lumen of the appendix showed a few organisms. Cultures yielded no growth. The fluid from about the cæcum and appendix showed no organisms on coverslips, nor did the scrapings from the serous surface of the ulcers. Cultures from this fluid yielded Bacillus subtilis and saprophytic bacilli.

Autopsy showed death from typhoid septicæmia. The peritoneal cavity was clean. The peritoneum was everywhere smooth and glossy, except where it was in contact with the gauze drain. Large swollen mesenteric lymph glands. Typhoid ulcers on lower 50 cm. of small intestine and on the upper portion of colon. No perforation.

Remarks.—It would seem impossible to make a definite diagnosis of appendicitis as the symptoms can not be distinguished from those of perforation. In this case it was clear that there was some acute process in the right iliac fossa and the condition undoubtedly demanded an exploration, but it is well known that this same region presents most frequently the signs of perforation. Even at the operation it was impossible to say whether the symptoms had not been in great part due to the condition of the intestines and the inflamed peritoneum, both parietal and visceral.

Directly beneath the point of greatest tenderness there was an area of inflamed parietal peritoneum, and directly beneath this two ulcerated Peyer's patches in the ileum. These patches were elevated on the serous surface and surrounded by a zone of prominent and tortuous lymphatics and blood vessels. The handling of this intestine caused the patient to complain of the severe pain which he had felt on pressure over this region before operation. The findings about the appendix, however, were undoubtedly due to an acute inflammation of this organ and entirely separate and independent of the condition in the ileum.

The question of acute appendicitis occurring in the course of typhoid fever and the importance of immediate operative interference has been discussed by Deaver.[1]

(c) *Intestinal Perforation.*

During the period covered by this report perforation of the intestine has occurred eight times, twice in association with intestinal hæmorrhage. Seven cases were operated upon; in the eighth operation was not advised on account of the hopelessness of the patient's

condition. Two have recovered and a third lived one week after the operation, dying then of profound toxæmia. Cases XII. XIII and XVII have been previously reported by Dr. Osler.[1]

Case XI.—*Typhoid fever; perforation of ileum on 11th day; operation; recovery.*

S. P. (Med. No. 11828; Surg. No. 10884), male, black, aged 38. Admitted to the medical side on Sept. 4, 1900, on the eighth day of typhoid fever. The Widal reaction was suggestive on the 8th day and positive on the 15th.

Sept. 5, Dr. McCrae.—On admission the patient is in good condition. The abdomen is rather full; respiratory movements present; some tenderness on the left side; spleen not felt.

Sept. 7, Dr. McCrae, 12.45 A. M.—The patient was seen by Dr. Cole at 12.15 A. M. and was crying out with abdominal pain. He was found on his back, sweating profusely, and looked as if he had had severe pain. The abdomen was natural, though the muscles were rigid.. Tenderness was complained of in the right hypogastrium and the patient definitely winced under pressure. Leucocytes, 3500 at 12.30 A. M. The patient stated that the pain had come on suddenly while on the bed pan. It began at the end of the penis and extended up into the abdomen.

1.30 A. M.—The patient lies on his back with legs extended. He states that he had been having some abdominal pain of a griping character on the previous day. There is nothing especial in his facial expression. The respirations are 26 to 33; pulse, 72; regular and small in volume. The abdominal respiratory movements are marked and even. In the lower right axilla dry coarse râles are heard at the end of inspiration. The abdomen is natural with no distention. The muscles on both sides are tense. On gentle palpation pain is elicited in the umbilical, right iliac, and hypochondriac regions. At times there are severe cramps, during which he will not answer questions. Liver dulness is absent in the right mammillary line and present for a hand's breadth in the right axillary line. The patient is dull and stupid and it is impossible to get a very accurate estimate of the pain he is having. He passed gas and fæces by the bowel a short time ago, and voided urine. Rectal examination is negative.

7.30 A. M., Dr. McCrae.—During the night the condition was much the same. Twice he had severe attacks of pain, in which the respirations rose to 50. At one time, 5.30 A. M., the abdomen was free from tenderness. He has hiccoughed several times during the night. At 7.30 this morning the condition is much the same as at 2 A. M. He is found on his side with the knees drawn up. Tenderness is noted as before. The abdominal walls are tense, but there is no muscle spasm. There is slightly more distention. His bowels moved at 4 A. M.

Surgical consultation (Dr. Mitchell) 9 A. M.—The abdomen shows more distention. The walls are more tense, and there is marked muscle

spasm, with tenderness over nearly the whole abdomen. Respirations, 24; pulse, 84.

Exploration was advised, but was delayed until 1 P. M. on account of another emergency operation.

Operation.—Mitchell; cocaine; chloroform; Sept. 7, 1900, 1 P. M. Laparotomy; suture of typhoid perforation in ileum; drainage; partial closure.

The patient was given ¼ gr. of morphia hypodermically before the operation. With Schleich's solution, an incision was made at the outer border of the right rectus, and the muscle retracted to the median side. On opening the peritoneum there was an escape of thin, brownish yellow, purulent fluid, and the distended intestines protruded from the wound. The patient was rather excited and whiffs of chloroform were given throughout the rest of the operation. The cæcum and ileum were drawn into the wound and the ileum explored, begining at the ileo-cæcal valve, the fluid in the peritoneal cavity, considerable in amount, being wiped away as the intestines were explored. Twenty centimeters from the cæcum was a perforation 1 cm. in diameter on the convex surfac of the ileum, sharply defined with clean cut edges, and looking as if punched out. The bowel about this was red and friable. From the perforation oozed thin fæces, a considerable amount of which had escaped into the peritoneal cavity. An attempt was made to close the perforation with a purse string suture, but on account of the friable condition of the bowel, mattress sutures were substituted, the direction of closure being in the transverse axis of the bowel. The rest of the ileum was carefully explored, only one other Peyer's patch being noticed. This was about 20 or 30 cm. from the perforation. The intestines were all considerably distended. In the pelvis was a large collection of pus and fæcal matter, which was carefully wiped out with gauze sponges. The upper abdomen and extreme left side were not disturbed being apparently free from pus, and the intestines showing less distention. There was some fibrin on the intestines about the perforation. There were no adhesions. A large iodoform gauze drain was placed in the pelvis and to the outer side of the cæcum. The intestines were replaced and the wound was partially closed with mattress sutures of silver wire.

The duration of the operation was less than an hour. The pulse rose from 100 to 130 during the administration of the chloroform. The patient stood the operation well and went to the ward in good condition.

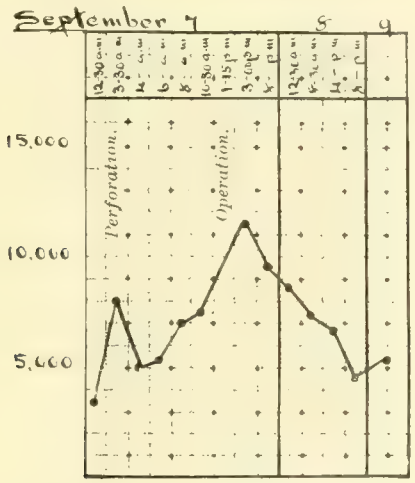
The head of the bed was elevated.

Sept. 9; Dr. Mitchell.—The patient has been perfectly comfortable since operation. His condition is steadily improving. There has been no vomiting. The pulse is 116; temperature 102.8°. To-day the temperature is 102.8°; pulse 94. He is taking his nourishment well. There is no pain or nausea.

Oct. 15; Dr. Mitchell. The patient's convalescence was uninterrupted. The gauze was gradually removed and the wound healed by granulation. He left the hospital well to-day.

Bacteriological notes.—Coverslips from the first fluid met in the peritoneal cavity showed no organisms; from the fluid in the pelvis, numerous bacilli. Cultures from the first fluid showed Bacillus coli communis. Cultures from the fluid in the pelvis showed Bacillus coli communis, proteus vulgaris, and other bacilli. No typhoid bacilli were obtained. No reaction of agglutination was obtained with any of these forms tested with the patient's blood. A positive reaction was obtained with Bacillus typhosus.

CASE XI. LEUCOCYTE CHART.



Remarks.—This case is especially instructive as we saw it from the beginning and constantly had perforation in mind. The case has to be studied in two periods—first, from onset about midnight (between Sept. 6 and 7) till 7.30 A. M. on the 7th; and secondly, after 7.30 A. M. During the first period the question was doubtful; in the second, the existence of a severe abdominal complication was clear.

Review of Symptoms.—Onset was sudden with complaint of severe pain, while the patient was on the bed-pan, beginning in the penis and extending into the abdomen.

Pain was very variable. At times there were severe paroxysms, during which the patient would not speak. With the pain

of onset there was profuse, clammy sweating. The pain did not increase as the symptoms progressed.

Facies showed nothing especial until 9 A. M.

Abdomen.—No distention until 9 A. M., i. e. for 9 hours.

Respiratory movements were *always* well marked. The walls had been held rather tensely since admission; they were somewhat more so during the night, but before 9 A. M. no muscle spasm was made out.

The tenderness was marked from the beginning, at first just to the right of the navel, and afterwards almost general. There was no dulness in the flanks.

Liver dulness was absent from admission in the right mammillary line and present throughout in the right axillary line.

Respirations increased in rate at once and remained high.

Pulse showed little change.

Leucocytes.—The possibility of the count of 8000 at 3.30 A. M. being the first wave of leucocytosis was considered, but the later counts did not seem to have any especial significance and no conclusions could be drawn from them.

Case XII.—*Typhoid fever; perforation of ileum on 16th day; operation; general peritonitis; death; autopsy.*

E. G. (Med. No. 12006, Surg. No. 11079), male, white, aged 24. Admitted to the medical service Oct. 11, 1900 in the first week of typhoid fever. The Widal reaction was positive at the time of admission. There have been some abdominal symptoms before admission, diarrhœa and abdominal pain.

Oct. 12, Dr. McCrae.—The patient looks as if he had been sick for some time. The heart sounds are feeble; pulse 112, regular and dicrotic. The abdomen is slightly full, everywhere soft; respiratory movements present. The spleen is readily felt.

Oct. 13, Dr. McCrae.—The patient is complaining of abdominal pain this morning. His general condition is much as yesterday. The abdomen is a little soft; respiratory movements free; muscles a little rigid; no spasm; no tenderness. Leucocytes at 9.30 A. M., 7000; 11.30 A. M., 5300; 3 P. M., 5100.

Oct. 15, Dr. Futcher.—The patient looks ill. The abdomen is slightly distended; muscles soft; no tenderness; no pain. Hepatic dulness reaches the costal margin.

Oct. 16.—Leucocytes, 2100.

Oct. 17.—There is considerable abdominal distention; no rigidity, tenderness or muscle spasm. Leucocytes, 1300.

Oct. 19, Dr. McCrae.—The patient was seen at 9.05 A. M., 15 minutes

after being taken out of a tub. He was complaining of severe abdominal pain; there was some cyanosis, and considerable shaking. These he has always had after tubs. The abdomen is more distended; the movements are free. Considerable pain is complained of to the right of the umbilicus. The muscles are very tense. This, however, varies considerably. There is no muscle spasm. At times fairly firm pressure can be made without the patient complaining of any tenderness. Liver dulness is obliterated in the median line but present in the axillary line. Leucocytes, 4000.

Oct. 19, 10 A. M., Dr. Futcher.—There is some dulness in the flanks; no muscle spasm. Leucocytes, 3400. 11 A. M.—The patient is more comfortable; less cyanotic. His nose is cold. The pulse is 100. There is no nausea or vomiting. He has had one attack of abdominal pain since 10 A. M. The respiratory movements are free, slightly limited below the umbilicus. The abdominal muscles are rigid; no muscle spasm. There is considerable pain and tenderness on pressure on the right side. Pressure causes sudden paroxysms of pain. Hepatic dulness extends to the costal margin. Rectal examination is negative. Leucocytes, 11.15 A. M., 5300; 12.20 P. M., 4000; 2.15 P. M., 4000; 3.15 P. M, 4200; 4.15 P. M., 5200.

2 P. M.—There is profuse sweating.

2.30 P. M., Dr. Futcher.—The abdomen is considerably more distended. There is still marked distention over the hypogastric region, though he complains less.

4.30 P. M., Dr. Futcher.—The patient is seen with Dr. McCrae and Dr. Mitchell. His condition is not materially changed. The pulse is still of good volume, but has increased slightly. He has hiccoughed once during the examination. There is no nausea or vomiting. A small amout of gas has been expelled through a rectal tube, but there is no decrease in the abdominal distention. There is still marked tenderness over the hypogastric and both iliac regions, pressure causing the patient to wince. The muscle rigidity is greater over the right rectus. The point of greatest tenderness has varied greatly during the day. There is no actual muscle spasm. Slight shifting dulness is made out in the flanks. There is no increase in the leucocytes, nor in respiration. The respiratory movements are slightly more limited than at the previous note. The following symptoms suggest the possibility of an intestinal perforation; sudden onset of pain about 9 A. M.; persistence of the pain; association with the tenderness on deep pressure; the muscle rigidity and the increasing abdominal distention; movable dulness in the flanks. Important symptoms of perforation often present which are now absent are: there is no drop in temperature; no especial increase in rapidity of the pulse; no nausea or vomiting; no symptoms of collapse; no obliteration of liver dulness; no muscle spasm; no marked diminution of respiratory movements; no leucocytosis. The patient is to be given the benefit of the doubt and an exploratory laparotomy to be performed.

The operation was done at 6 P. M., 9 hours after the sudden onset of abdominal pain.

Operation.—Mitchell, Oct. 19, 1900; cocaine; chloroform. Exploratory laparotomy. Purulent fluid and gas in the peritoneal cavity. Closure of typhoid perforation in ileum; drainage; partial closure.

An incision was made at the inner border of the right rectus muscle, and the muscle retracted to one side. Immediately on opening the peritoneal cavity there escaped a large quantity of purulent fluid with gas. The intestines were much distended, especially the colon, cæcum, and the sigmoid flexure. The ileum was explored, beginning at the ileo-cæcal valve. Twenty centimeters from the cæcum there was a perforation 4 mm. in diameter in the centre of an ulcerated Peyer's patch from which escaped gas and yellow fæces. The fluid in the peritoneal cavity was thoroughly wiped out with gauze sponges and the perforation was closed with a purse string suture of silk, reinforced by mattress sutures. One centimeter from the cæcum in the ileum there was an angry looking Peyer's patch, over which the serosa was desquamated. This was likewise turned in with a purse string suture of fine silk. The vessels of the distended intestines were injected, all of the intestines having a general pinkish color. The bladder was distended and its serosa injected. There was an extensive fresh peritonitis throughout the lower portion of the abdomen. The pelvis was filled with purulent fluid. The appendix was negative. The intestines were withdrawn loop by loop and wiped off with salt sponges. The pelvis and lower portion of the peritoneal cavity were likewise wiped out. An iodoform gauze drain was placed to the bottom of the pelvis and to the sutured intestine. A rectal tube was inserted to relieve the distention. The wound was partially closed with silver wire. The operation was begun with cocaine and lasted an hour and ten minutes. During the last half hour whiffs of chloroform were given as the patient was restless and complaining, but at no time was he deeply anæsthetized. There was some rise in the pulse rate after the administration of chloroform, although it had remained low as long as cocaine alone was used.

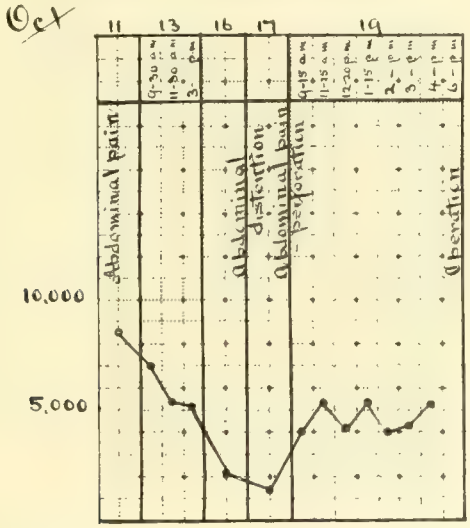
Sept. 20.—The patient's condition has remained about the same since the operation. The pulse is rapid and weak; temperature about 101°, somewhat lower than before operation. He has been complaining of abdominal pain, paroxysmal in character, especialy in the upper abdomen. There has been no vomiting and no nausea since the operation. The abdomen is less distended, the distention being principally in the upper portion. The patient seems hypersensitive, crying out when touched and at times allowing deep pressure with apparently no pain. The abdomen is soft, no muscle spasm. The drains are discharging freely.

Oct. 22, Dr. Mitchell.—The patient's distention and abdominal pain were somewhat relieved by turpentine stupes and enemata, large

quantities of flatus being passed. On Oct. 21, the abdominal pain still continued; the distention was increased; the respirations remained rapid. There was considerable vomiting throughout the day. The distention was not relieved by turpentine by mouth and in stupes and enemata. The possibility of intestinal obstruction from the drainage or from adhesions seemed to justify the opening of the wound. A few whiffs of chloroform were given and the wound was opened. There was considerable pus about the gauze drainage. No definite obstruction was found, only a general distention and paralysis of the bowels, due to the peritonitis.

The patient's condition was not affected by the exploration, his abdominal symptoms increased, aand he died this morning at 9 o'clock.

CASE XII. LEUCOCYTE CHART.



Bacteriological notes.—Coverslips from the fluid in the peritoneal cavity showed bacilli; from the seat of perforation, all sorts of organisms with some streptococci. Cultures from the urine gave a bacillus of the typho-colon group. Cultures from the peritoneal cavity yielded Streptococcus pyogenes and a bacillus of the typho-colon group, which would not agglutinate with the patient's or with another typhoid patient's serum.

Autopsy.—General acute sero-fibrinous peritonitis. Typhoid fever; ulceration of the ileum. Acute splenic tumor; cloudy liver; swelling of kidneys; hyperplasia of mesenteric lymph glands. The intestinal sutures had held.

Remarks.—The onset was very sudden and decided. The patient cried out with severe pain, which he referred principally to the penis. The subsequent pain was paroxysmal, sharp in character, and coming on without handling of the abdomen. There was no sign suggestive of shock. The pain was very great in severity and was referred to the lower hypogastrium.

Tenderness present from the onset varied in amount and situation, but was fairly constant in the lower hypogastrium.

Respirations were practically unchanged, usually 26.

Abdomen.—At the onset at 9.05 A. M. there was more rigidity than at any later period. It was not constant. *Respiratory movements* were a little less marked in the morning. Distention increased rapidly during the afternoon. It had been noticed that in this patient the abdominal symptoms were marked throughout his whole illness, and he was carefully watched for the signs of a perforation. The delay in recognizing the condition can be attributed partly to the severity of the abdominal symptoms throughout his whole illness. His death was due to general streptococcus peritonitis.

Case XIII.—*Typhoid fever; perforation of ileum on 18th day; operation; protrusion of intestines from wound; operation; recovery.*

F. A. R. (Med. No. 12202, Surg. No. 11272), female, white, aged 8. The patient was admitted to the medical service on Nov. 22, 1900, on the 5th day of typhoid fever. The Widal reaction was positive on the following day.

F. H.—Her mother died of typhoid fever three days before the admission of the child, one sister died of typhoid fever 13 days ago; another brother and sister are convalescent.

She had felt badly for two weeks preceding admission. There had been diarrhœa; no epistaxis; no herpes; no vomiting. The attack was a severe one. She had 80 tubs during her stay on the medical side. The temperature was very high, reaching 105.4°.

On admission the leucocytes were 4500 and on Nov. 24, 4600.

On Nov. 25, she began to have abdominal pain. There was no distention. The abdomen was soft. The leucocytes were 8200. The pain was relieved by turpentine stupes. There was no vomiting or nausea.

On Nov. 26, there was some distention and general abdominal tenderness and pain, but no muscle spasm. The leucocytes at 8 A. M. were 11,400; at 2.30 P. M., 9300.

On Nov. 27, the leucocytes were 11,000, and on Nov. 28, 9800.

Nov. 30.—There was still some slight distention.

Dec. 4.—The leucocytes are 6200. The temperature is still high. The patient's general condition is good. The abdomen is very soft and nowhere tender. The spleen is readily felt.

Dec. 5.—The condition is about the same. In the morning the leucocytes were 5500.

10 P. M., Dr. McCrae notes that the patient had a tub at 6.10 P. M. At 7.15 she cried out with pain, localized in the right iliac fossa. The pulse was very small, of low tension, dicrotic and rapid. The abdomen was slightly more distended and held rather firmly but without muscle spasm. At 7.30 the leucocytes were 11,500; at 8.30, 8300. Turpentine stupes were applied to the abdomen and the patient fell asleep. 10.15 P. M. She is sleeping quietly.

11 P. M., Dr. Futcher.—The child was found on her right side, her thighs flexed, not complaining of pain. On being turned on her back she cried out with pain below the navel. The temperature was 102.8° at 10 P. M. She has not vomited. The pulse is regular, 128. The abdomen is distinctly distended. Respiratory movements are free throughout, perhaps somewhat limited below the navel. There is quite marked general rigidity of the abdominal muscles and rather decided muscle spasm over the right rectus, but no definitely localized tenderness. There is no definite dulness in the flanks. At 11.40 P. M. the leucocytes are 7500.

Dec. 6, 1 A. M., Dr. Futcher.—The abdominal pain has persisted since last note. At times the patient cries out with the intensity of it. There is slight "risus sardonicus." The pulse is weaker, now 152. She has not vomited. The abdominal distention is not increased, but the tenderness is now very marked and causes her to cry out on the slightest pressure. Respiratory movements are less than two hours ago. There is movable dulness in both flanks. There is marked rigidity and muscle spasm. The liver flatness is obliterated in the mammillary line. The symptoms are extremely suspicious of perforation.

1 A. M., Surgical consultation, Dr. Mitchell.—Conclusion, probable perforation. Immediate exploration is advised.

Operation.—Dr. Mitchell; Dec. 6, 1900, 2.30 A. M.; cocaine and chloroform. Laparotomy; closure of typhoid perforation in ileum; drainage; partial closure.

The patient was given ⅛ gr. of morphia, hypodermically in the ward, and 1/10 gr. just before beginning the operation. She was much quieted by this. The operation was begun with Schleich's solution. This was used for the skin incision and until the posterior sheath of rectus was reached when whiffs of chloroform were administered. An incision was made at the outer border of the right rectus muscle, the anterior and posterior sheaths divided, and the muscle retracted towards the median line. Immediately on opening the peritoneum there escaped a considerable amount of cloudy yellow,

bile-stained, odorless fluid. There was a large collection of purulent fluid in the right iliac fossa and in the pelvis. This was wiped away with salt sponges. The cæcum was sought and with the ileum withdrawn from the wound. The cæcum, appendix and colon were distended. The small intestine was not distended, pinkish in color, somewhat injected, the smaller vessels being rather prominent. In the mesentery about the cæcum and ileum were many hard, enlarged, lymph glands, and adhering to the cæcum were flakes of yellowish fibrin, which were easily brushed away with gauze sponges. In the ileum about 10 cm. from the cæcum there was a perforation 2 mm. in diameter, clean and punched out in the middle of a not very prominent ulcer. From it escaped a quantity of clear golden yellow, bile-stained fluid. The intestinal wall was covered with fibrinous exudate. The ulcer was about 1½ cm. in diameter. There were many more in the ileum, one or two angry looking, and the lower part of the bowel near the cæcum had a bluish appearance. No other perforations were seen. The intestines on the right side were withdrawn and irrigated with salt solution. The peritoneal cavity, especially the pelvis and the right iliac fossa, were wiped out with salt sponges. The omentum was pulled down and sutured over the perforation and the ulcerated portion of the ileum after the replacement of the intestines. A strip of iodoform gauze was placed in the pelvis, another to the suture, and a third about the omentum. The wound was partially closed with mattress sutures of silver. The patient stood the operation well. The pulse was good at the end. The duration of the operation was one hour. The patient was placed in bed with her head elevated and was given an enema of salt solution and coffee. The leucocytes were 7500; temperature 102.8°; pulse 160.

The temperature gradually fell to normal, and then rose again and remained between 100° and 104°. The child ran a mild course of typhoid fever. The bowels moved on the second day after the operation. On the third day a part of the gauze was removed.

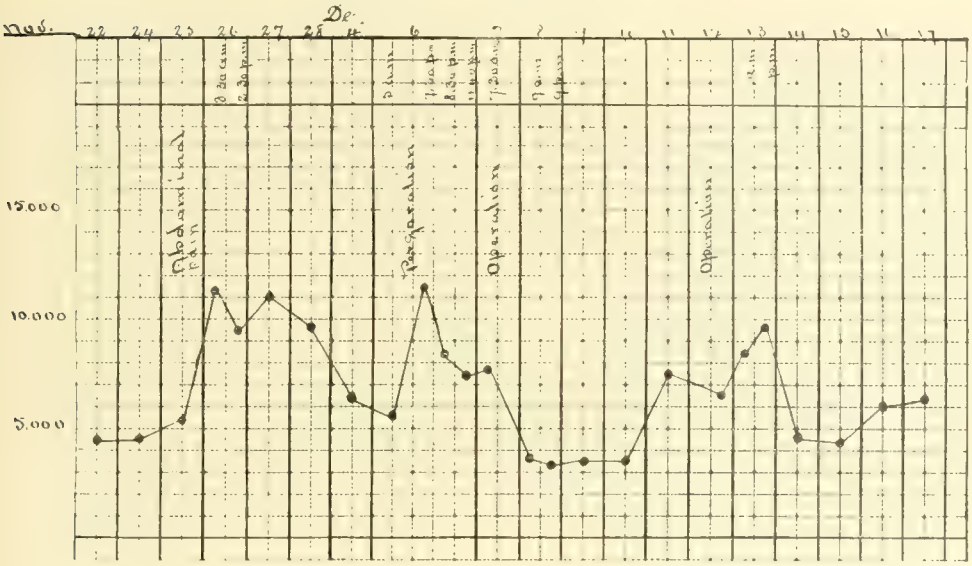
Dec. 11, 1900.—The gauze was partially withdrawn. There seems to be little reaction about it, a piece of omentum having been pushed out by the gauze packing. The patient has a troublesome cough.

Dec. 12.—The patient has been coughing a great deal during the past two days. This morning at 7 A. M. she complained of pain in the region of the wound. Examination showed a loop of intestine, which had protruded from the wound and was projecting from the lower edge of the dressing between the thigh. The bowel was healthy looking, but somewhat injected. Chloroform was administered and the bowel thoroughly cleansed with salt solution, and replaced. The loop was about one foot long. The wound was packed with a bismuth gauze pad and the abdominal wall tightly strapped with adhesive plaster.

Dec. 13.—She did well after this second operation. It seemed to have little or no effect on her general condition. Recovery was slow

but uneventful. The wound healed by granulation. She was discharged well on Feb. 23, 1901.

CASE XIII. Leucocyte Chart.



Remarks.—The onset in this case was with severe pain, which was paroxysmal in character. Fortunately, night rounds were being made at the time of onset of one of these attacks and attention was thereby drawn to the patient. Had it been a few minutes later when this pain was over and the patient not complaining, the condition might not have been recognized until the next day. For some days before this the patient had complained of abdominal pain, with which there bad been leucocytosis but no very marked local abdominal symptoms. The pain with the perforation was much more severe. It was more or less constant, but with exacerbations of great severity. The local abdominal symptoms were well marked. The tenderness, muscle spasm, diminished liver dulness, without any great increase in the distention, and movable dulness in the flanks seemed almost conclusive.

The sudden increase in the leucocytes is to be noted but the fact that this had also occurred before the perforation rather diminished its value. Operation was done about eight hours after the perforation.

Case XIV.—*Typhoid fever; perforation of ileum on 30th day; operation; improvement; death one week after operation; no autopsy.*

T. T. (Medical No. 13421), white, male, aged 11, was admitted to the medical service Sept. 9, 1901, on the 26th day of typhoid fever. The temperature was 102°, rising to 104°. The Widal reaction was suggestive on the day after admission.

Sept. 10, 1901, Dr. McCrae.—The boy looks as if he had been ill for some time. The abdomen is soft and rather full; respiratory movements present everywhere. The spleen is not felt. Leucocytes, 5500.

Sept. 11, Dr. McCrae.—The patient is having a good deal of delirium. Heart sounds are clear; pulse dicrotic; abdomen everywhere soft.

Sept. 13, 3 P. M., Dr. McCrae.—The patient this morning seemed as usual and was given a tub at 11.45. After he had been in the tub about five minutes, he suddenly cried out with pain. Between noon and 3 P. M. his bowels moved six times, the movements being accompanied by pain; loose, watery stools; no blood. At times he cried out during movement of the bowels.

At 3 P. M. he was found on his back, complaining of abdominal pain and objecting to being touched. The facies shows no change; always rather drawn. Respirations are free; pulse 144, small and running. The abdomen is flat and symmetrical; respiratory movements well marked. On palpation there is everywhere some tenderness, more on the right side. He cries out on more than the slightest pressure in the right iliac fossa. There is no rigidity nor muscle spasm on the left side. On the right there is some resistance to pressure in the iliac fossa. Liver dulness is absent in the middle and right nipple line. In the midaxillary line it begins at the eighth rib and extends to the costal margin; no dulness in the flanks. Rectal examination is negative. The abdomen is everywhere tympanitic. Leucocytes, 1 P. M., 5700; 3 P. M., 5200; 4.30 P. M., 8000.

Sept. 13, 4.30 P. M.—The patient is asleep; respirations 37; pulse 134. On awaking he does not complain of pain. There is no special change in the facies. The abdomen is practically the same; slight retraction; respiratory movements especially well marked. On first examination the fingers could be sunk deeply in the right iliac fossa without causing muscle spasm. After handling, some rigidity of the right rectus appeared. Liver dulness was unchanged. When left alone he would slowly pull up one leg and then the other, and remain with the legs doubled up, with the hands crossed over his chest. There is no suggestion of phlebitis.

5.30 P. M.—Leucocytes, 12,000.

6 P. M.—The boy looks much worse and is duller. Respirations are 40; pulse 140, small and running. The abdomen is much the same, but the respiratory movements are markedly diminished below the navel. There is definite tenderness in the right iliac fossa and well marked muscle spasm. Liver dulness is slightly diminished in the

mid-axillary line; no dulness in the flanks. Auscultatory percussion is negative.

At this time the diagnosis of perforation seemed justified. The sudden onset of pain, which had occurred in paroxysms at first with rise in respiration and pulse, diminished liver dulness with a flat abdomen, and increase in leucocytosis were likely signs, which seemed to support it.

Opposed to the diagnosis of perforation were the facts that in the afternoon there was little pain; the respiratory movements were well marked; there was no distention, and there was profuse diarrhœa which might have caused some of the symptoms.

The leucocytes were 12,500 at 6.45 P. M.

7 P. M.—There is considerable change since 6 o'clock. The boy looks worse; pulse and respiration much the same; abdomen decidedly fuller; respiratory movements less, almost gone below the navel.

Surgical consultation, 7.30 P. M. (Dr. Finney).—The patient is quiet. He looks worse but makes no complaint. The abdomen is slightly distended. Respiratory movements are slightly less than at 7 P. M. There is considerable rigidity and marked muscle spasm. Dr. Finney agreed as to immediate operation.

Operation.—Dr. Finney; cocaine. 8 P. M., 8 hours after perforation. Laparotomy; suture of typhoid perforation; partial closure; drainage.

An incision was made through the right rectus muscle. The peritoneal cavity contained 500 cc. of turbid yellow fluid and considerable gas. The ileum was sought and at a point about 18 inches from the cæcum was a perforation in an ulcer surrounded by a reddened, indurated area. The perforation was closed by mattress sutures of fine silk. The coils of intestine in the upper half of the abdomen were not involved. Those in the region of the perforation were injected, reddened and had lost their lustre, and in places were covered by fresh exudate. The pelvis was full of thin, turbid fluid. The pelvis was wiped out, irrigated with salt solution, and the involved coils were wiped and washed with salt solution and replaced. An iodoform gauze drain was placed in the pelvis. The wound was partly closed with silver wire, the omentum being brought down over the sutured intestine. The patient stood the operation well, its duration being one-half hour.

Sept. 14.—After the operation at 2 A. M. the patient was in a state of low delirium with tremor of the lips, and grating of the teeth; pulse 172; respirations deep and jerky. He was delirious all day.

Sept. 15.—The abdomen is everywhere soft and free from tenderness.

Sept. 19.—Since operation the temperature has ranged from 102° to 106°. There have been no vomiting or abdominal symptoms. The

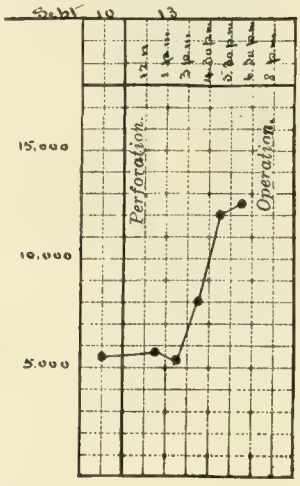
drainage has been removed and the wound is clean. The patient is delirious, picking at his dressings and bed clothes.

Sept. 20.—The patient in his delirium pulled out the skin sutures. At 7 P. M. yesterday he complained of severe abdominal pain. The respirations became more rapid and labored. About 10 o'clock his condition began to grow worse and he died at midnight.

Bacteriological notes.—Bacillus coli communis was obtained in cultures from the fluid in the peritoneal cavity.

No *autopsy* was obtained.

CASE XIV. Leucocyte Chart.



Remarks.—Perforation occurred probably at 12 noon on Sept. 13, with the sudden onset of pain. The pain was sudden and severe at the onset, and recurred at intervals of about three hours, apparently only with the movements of the bowels. After 4 P. M. there was little complaint of pain, except on palpation. Respirations increased almost at once and at 3 P. M. they were only 24; but usually over 30. The pulse had increased. Since admission the pulse had been rapid, small and running.

Bowels.—Frequent movements, six in three hours; thin and watery. Considerable pain with each.

Hiccoughing and vomiting, none.

Facies.—The boy had looked badly since admission, emaciated and sick with a sallow, grayish color. There was little change before the operation.

Temperature remained elevated.

Leucocytes increased 4½ hours after perforation to 8000; and 5½ hours to 12,000.

Abdomen flat and slightly excavated until about 6 P. M., after which it became level and was at 7.30 slightly full. The respiratory movements were marked until 6 P. M. Then they rapidly became limited, first below the navel. There was marked general tenderness at 3 P. M.; later there was little or none. There was no special local tenderness until about 6 P. M. and no definite or constant muscle spasm or rigidity was made out during the first six hours. Liver dulness diminished at 3 P. M. with an undistended abdomen; no special change until after 6 P. M. No dulness in the flanks was made out at 4.30 P. M. Auscultatory percussion was of no assistance. Rectal examination was negative.

It is seen that the symptoms can thus be divided into two periods, those during the first six hours, and those during the second two hours. Six hours after perforation there was a definite change, after which time all the signs and symptoms were much more definite.

At the operation we were very hopeful of recovery as the process in the abdomen was comparatively local. As far as the peritonitic condition was concerned he did perfectly well. Death at the end of a week resulted from the toxæmia due to the severity of the disease. It may be correctly said that the perforation and operation were only incidents in the course of the attack and did not contribute to the fatal issue.

Case XV.—*Typhoid fever; myoma of uterus; bronchitis; perforation of ileum on 16th day; operation; death; no autopsy.*

M. A. G. (Medical No. 13943, Surg. No. 12943), female, black, aged 30, was admitted to the medical side Jan. 19, 1902 at 7 P. M. with the family physician's diagnosis of pneumonia. The patient was taken ill on Jan. 6, 22 days before admission, and a day or two afterwards her doctor told her that she had pneumonia. She was put to bed and kept on a milk diet. Her condition has remained about the same. She does not think she had fever; no chills; no herpes; no nose bleed; no vomiting.

Jan. 20, 1902, Dr. McCrae.—The temperature was 103°, rising rapidly to 104.5°; pulse 100, small and regular. The patient looks very ill; seems dull and stupid; breath foul; tongue coated and dry; respirations 24; no dyspnœa.

Chest.—Expansion is slight; breath sounds are feeble over lower right axilla and back. Over both sides an occasional piping râle is heard; otherwise there is nothing definite. The heart sounds are feeble.

Abdomen is prominent below the navel where there is a round, hard, solid mass filling the pelvis, probably a myoma uteri. The spleen is not felt. There is no pain. The Widal reaction is positive. The leucocytes are 15,800.

Jan. 20, 10.15 P. M.—The patient complained suddenly of abdominal pain about 9.30 to-night. When seen during the day she had been slightly delirious and did not answer questions very intelligently. The attention of the nurse was called to her by her crying and groaning. At 10.15 she was found on her back, knees drawn up, at times groaning slightly. She made no intelligent answers to questions but placed her hand over the abdomen. The facies showed nothing very suggestive; respirations 36, very shallow. No especial change is made out in the lungs. The breath sounds are feeble and the piping râles heard in the morning are not obtained. There is no friction rub. The pulse is 124, of small volume, regular and easily compressed. The abdomen is rather full, especially below the navel, but not more so than in the morning. Respiratory movements are present but only above the navel, being completely absent below. On palpation there is marked tenderness, the patient both complaining and showing signs in her face of pain. Great tenderness is elicited by pressure in the right side below the navel. There is no muscle spasm, although the rigidity is considerable. The large tumor had some influence upon this. This is in marked contrast to this morning when the walls were perfectly lax. The percussion note in the right flank has definitely less resonance than on the left side. The condition very strongly suggests perforation.

Surgical consultation.—10.30 P. M., Dr. Mitchell. The patient is exceedingly dull and stupid. The abdomen is not distended except in the suprapubic region where there is a hard, solid tumor, filling the lower abdomen, evidently a myoma uteri. Rectal examination is painful. There is marked tenderness over the whole suprapubic region, becoming greater as the right iliac fossa is reached and attaining its greatest intensity about McBurney's point. There is no muscle spasm, although the patient cries out when palpation of this region is attempted. There is some resistance, apparently voluntary, of the abdominal muscles. The condition can be accounted for only by some acute intra-abdominal trouble, most probably a perforation, although an appendicitis or a salpingitis cannot be differentiated on account of the presence of the myoma. Immediate exploration is advised.

Leucocytes, 10.45 P. M., 14,300.

Operation.—Mitchell; cocaine. Laparotomy; closure of typhoid perforation; drainage.

The patient was given ¼ gr. of morphia hypodermically in the ward and immediately brought to the operating room. The abdominal condition on the table was about the same as when examined in the ward. Incision was made at the outer border of the right rectus muscle, and the muscle retracted to the median side. On opening the abdomen there escaped cloudy fluid, becoming thicker as the pelvis was approached. Presenting just within the incision was the ileum, and in it a perforation in the middle of a large Peyer's patch. The coil of ileum was brought up and the perforation closed with a purse string suture, reinforced by mattress sutures of fine silk. The fluid was wiped out of the pelvis and the region of the cæcum drained with three or four iodoform and protective wicks. The patient did not complain during the operation, but the outlook seemed rather hopeless on account of her grave general condition. The time consumed on the operating table was about one-half hour, preparing the patient, closing and dressing the wound. The pulse was not affected by the operation.

The temperature just before the operation was 104.6°. It rose to 106° four hours afterwards and remained high. The pulse did not increase in rapidity but gradually became weaker, and she died at noon on Jan. 21. No autopsy was obtained.

Bacteriological notes.—Cultures from the fluid in the peritoneal cavity yielded Bacillus coli communis; from the contents of the bowel, at the point of perforation, Bacillus coli communis and Streptococcus pyogenes.

Remarks.—Review of symptoms:

The *Onset* seems to have been sudden, although there was some pain complained of between 8 and 9 P. M. The symptom to attract attention was the complaint of pain.

Pain was evidently severe. The patient had been very dull and drowsy early in the day, but in spite of this she groaned with the pain. It was not continuous but paroxysmal. It was fortunate that she was having one of these paroxysms when the resident physician came into the ward, as otherwise the gravity of the condition might not have been so strongly impressed upon him.

Abdomen.—There was no distention apart from that due to the myoma.

Respiratory movements were present above but absent below the navel and apparently rather less than they had been in the morning.

Pain was referred to the neighborhood of the umbilicus.

Tenderness was marked with any pressure, more on the right side below, the greatest tenderness being in the right iliac fossa.

Rigidity was not marked but slight on firm palpation.

Muscle spasm was not present.

Liver dulness was present and not especially diminished.

Flanks—some dulness in the right. The patient was not turned to make out the presence of shifting dulness.

Respiration perhaps slightly increased but not markedly.

Pulse rate was somewhat higher but no especial change.

General appearance.—There was nothing very striking when quiet but marked distortion as with pain followed when the abdomen was palpated. The most striking thing was the finding of the patient with the legs drawn up, groaning with pain, which increased greatly on palpation—a picture seen in typhoid fever usually only with perforation.

Leucocytes—no especial change. Only one count was made before operation after the symptoms began.

Bowels—apparently no movement or expulsion of flatus after the perforation.

The operation was done only three and a half hours after perforation. The peritonitic condition offered the most favorable prognosis. The operation was short and had no effect on the patient's general condition. Death can be attributed to the general typhoidal condition. The patient was extremely ill on admission and a grave prognosis had been given before the occurrence of perforation.

Case XVI.—*Typhoid fever; intestinal hæmorrhage; perforation of ileum on the 25th day; operation; death; autopsy.*

H. D. (Medical No. 14250, Surg. No. 13284), male, white, aged 27, was admitted to the medical side on April 11, 1902, on the 15th day of typhoid fever.. His temperature on the day of admission was 104.6°, and the leucocytes, 4500. The abdomen was soft, natural, not distended; there was no tenderness. The general condition was good. The Widal reaction was positive on the day of admission. Bacillus typhosus was obtained from the blood on the following day. During the next ten days the temperature was high, ranging from 103° to 105°. There were no abdominal symptoms. The daily count of leucocytes averaged from 3000 to 6000.

April 20.—The patient had two intestinal hæmorrhages, one at 2 P. M., consisting of 600 cc. of changed blood, in which there was an adult Ascaris lumbricoides. Leucocytes, 11 A. M. 5400; 5 P. M., 5600; 11.30 P. M., 6000. The patient complained at noon, that is at the time of the first hæmorrhage, of some pain in the right side.

April 21.—The general condition is good; abdomen negative; leucocytes, 3 P. M., 7000; 5 P. M., 7500.

At 5 P. M. the patient complained of intense abdominal pain. A few moments later he passed 500 cc. of changed blood. There was a severe shaking chill. He was sweating profusely. The pulse became small, almost running, 160; and the respirations, rapid. The abdomen was more distended, but the respiratory movements were free throughout; some rigidity of the muscles; no muscle spasm. The temperature rose from 103.2° to 106°. After the chill, at 6 P. M., the pulse became soft and full and remained about 160. He was seen at this time in surgical consultation and his symptoms supposed to be due to the hæmorrhage, although the possibility of a perforation was considered.

7 P. M., Dr. McCrae.—The patient is found sweating profusely; no especial change in the facies. The abdomen is natural, not distended; respiratory movements free. The walls are soft; no tenderness; no muscle spasm; no rigidity. No liver dulness can be made out in the median or parasternal lines. In the right mammillary line there is no absolute dulness. In the mid-axillary line the dulness begins at the 7th rib and extends almost to the costal margin.

8 P. M., Dr. Osler.—The pulse is rapid and quiet. Respirations are rapid. There is no pallor, but profuse sweating. There is complete absence of liver dulness in the mammillary line. Opium is ordered in ½ grain doses every four hours.

April 22, Dr. McCrae.—The temperature has fallen from 106° last night to 99.7° this morning. He has passed no more blood by rectum. The abdomen is somewhat more distended; the walls are more tense. Respiratory movements are still well marked. The pulse is 108, soft and full. Blood pressure is 93 mm. Leucocytes, 10,600.

9.45 A. M., Dr. Cole.—This morning the patient is sweating profusely and has been perspiring since 6 P. M. He is rational; slight cyanosis of ears and lips; occasional hiccoughing; no vomiting. The abdomen is considerably distended; respiratory movements free, rather limited below the umbilicus. The walls are held firmly; no rigidity; no muscle spasm. The lumbar flank muscles are very rigid. There is no inequality of resistance on the two sides and no extreme tenderness anywhere. At 11.15 A. M. the leucocytes were 11,200.

12 noon, Dr. Osler.—The respirations are slow from opium. The pulse is distinctly better. The abdomen is a little less tense; no pain or special tenderness; no special pain on palpation. Leucocytes, 11,100.

1 P. M.—Leucocytes, 8200.

2 P. M., Dr. McCrae.—The patient lies usually with his knees drawn up; rather dull and stupid; sweating profusely. The respirations are slow, probably due to opium, which he had from 8 P. M. until 9 A. M.; pulse, 108. The abdomen is fuller; the respiratory movements rather well marked. There is marked rigidity. The walls are tense; no special tenderness; no muscle spasm; no increased resistance in the right iliac fossa. Liver dulness is almost absent. Leucocytes, 14,400.

At 4 P. M. he was seen in surgical consultation. Leucocytes, 14,400.

The patient's symptoms are much more definite. There is a distinct change in the facies, suggesting a peritonitic character. The nose looks pinched. The abdomen is less distended; still rigid, and the tenderness is general and marked; distinct muscle spasm on the right side. Operation is decided upon. Leucocytes, 14,100. 5 P. M., leucocytes, 14,600.

Operation.—Mitchell; cocaine. Laparotomy. Suture of typhoid perforation in ileum. Cleansing of pelvis. Drainage.

An incision was made through the right rectus muscle with 1-3000 cocaine. Immediately on opening the peritoneum there escaped a large quantity of foul smelling, purulent fluid from the right iliac fossa and pelvis. There was a large amount of this which was wiped away with gauze sponges. The bowels were not distended. The ilium and cæcum were immediately sought and examined. The appendix was negative. The ileum was followed up from the cæcum and at a distance of 35 cm. on an angry-looking coil of intestine was a perforation in the middle of a swollen, bluish Peyer's patch. The perforation was about 3 mm. in diameter and from it escaped gas and fæces. The perforation was closed with a purse string suture of fine silk, reinforced by a couple of mattress sutures. Near this ulcer was another which looked as if it were about to perforate. The area, however, was too large to turn in. The rest of the abdomen appeared free from peritonitis and was not disturbed. The right iliac fossa and pelvis were thoroughly wiped out. No other perforations were found. A strip of iodoform gauze was placed to the site of the suture and the angry looking bowel. The omentum was pulled down over this region. Iodoform and protective drains were placed leading to the pelvis. The wound was partially closed with silver. The patient stood the operation well, complaining not at all, the blood pressure varying but little. He went to the ward in apparent good condition. The temperature had fallen gradually during the night before, and at the time of operation was normal, having been for a few hours previously subnormal. After operation it rose to 100°; pulse 114, good quality.

April 22, midnight, Dr. Mitchell.—The patient has been hiccoughing during the evening. His bowels moved slightly after a turpentine enema. The stomach was washed out to relieve hiccoughing.

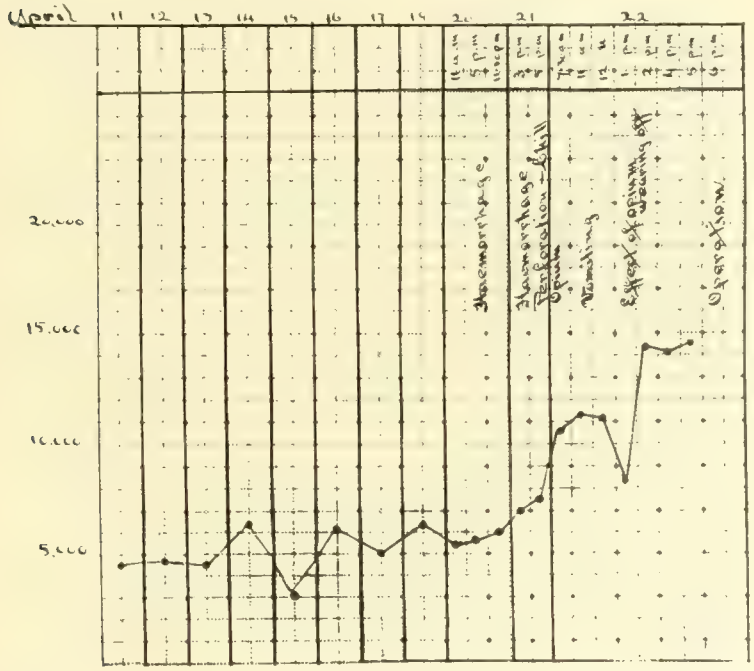
April 23, 10 A. M., Dr. Mitchell.—The patient was rather restless during the night. His hiccoughing was relieved by stomach lavage and he was much more comfortable; dozing at intervals; very thirsty. The hiccoughing began again about 4 this morning, and has been very annoying. The stomach lavage was repeated, a great deal of bile stained fluid being removed. Four ounces of Epsom salts were run in through the stomach tube. The abdomen is soft. There is little tenderness. He complains of no pain. His general condition is fairly good. Temperature, 100.4°; pulse 120, good volume.

5 P. M.—The temperature began to rise during the morning; at noon, was 101.5°; 2 P. M., 103.4°; 4 P. M., 104.6°. During the afternoon the

patient's condition changed rather suddenly. His pulse became weaker and irregular; respirations labored. He was restless and picking at the bed clothes. He gradually became weaker and died at 4.45 P. M.

Autopsy.—Anatomical diagnosis—typhoid fever; ulceration of ileum. Parenchymatous degeneration of viscera. Splenic tumor. Diffuse peritonitis. Emphysema of all organs. The peritoneal cavity at autopsy looked very clean. There was no spread of the peritonitis, which was more or less limited to the right iliac fossa. The field of operation looked clean. The intestines were not distended.

CASE XVI. LEUCOCYTE CHART.



Bacteriology.—Bacillus typhosus was obtained from the heart's blood, bile, spleen, liver, peritoneal cavity and mesenteric glands; Bacillus coli communis from the heart's blood, liver, mesenteric glands, kidneys and omentum; Streptococcus pyogenes from the liver; Staphylococcus pyogenes aureus from the peritoneal cavity; Bacillus aërogenes capsulatus from the heart's blood, liver, spleen, kidneys and mesenteric glands.

Remarks.—The probability is that the perforation occurred at 5 P. M. on April 21. When seen at 7 P. M. the general appear-

ance should have carried more weight. This suggested some marked change, although the abdomen was negative.

On the 22d there were several confusing facts. The opium had masked the symptoms. The abdominal features were slight and the pulse had become markedly better. At 11 P. M. on the 21st it was 144, of poor volume and tension, while on the 22d it had fallen to 108 and was of decidedly better volume. To take up the symptoms in detail:

Onset.—If this was at 5 P. M. on the 21st, which seems probable, it was sudden, associated with severe acute pain and an intense shaking chill.

Facies.—This was striking at the time of onset and shortly after, principally on account of the profuse sweating. Otherwise there was no special change until about 4 P. M. on the 22d.

Hiccoughing.—Some occurred on the 22d, which might have been explained by the abdominal distention.

Vomiting.—Occasional during the 22d, once after the taking of a dose of turpentine.

Respirations.—These showed no special change; rose to 28 at midnight on the 21st, but were slow on the 22d, averaging about 20.

Pulse.—This was markedly affected at the onset on the 21st, rising from 100 at 4 P. M. to 160 at 6 P. M. This we thought was probably due to the hæmorrhage. Afterwards the volume and tension became better, which was very misleading.

Abdomen.—Distention was moderately marked on the 22d in the morning; rather less marked in the afternoon. The respiratory movements were good throughout, both above and below the navel. Rigidity was marked with the distention on the 22d. Muscle spasm was only obtained at 4 P. M. on the 22d after the effects of the opium had worn off.

Liver dulness was much diminished after the onset on the 21st. No special change afterwards, except slight diminution in the mid-axillary line.

Percussion.—Auscultatory percussion was negative. There was some dulness in the right flank throughout.

In considering the abdominal symptoms, two things have to be kept especially in mind—first the occurrence of hæmorrhage, and second the opium given from 8 P. M. on the 21st to 9 A. M. on

the 22d. A very unusual feature in this case was the severe chill at onset with a sudden elevation of temperature from 103° to 106°. After the chill there was almost a continuous drop. This is the only case in which we have observed a chill at the time of perforation, whereas a chill, or at least chilly sensations, with hæmorrhage is more or less common.

CASE XVII.—*Typhoid fever; intestinal hæmorrhages; perforation of ileum on 15th day; operation; death; no autopsy.*

W. S. (Med. No. 12149), male, aged 21 years, was admitted to the medical service on Nov. 10, 1900 on the 9th day of his illness. He had come several hundred miles by rail. The Widal reaction was given on the day of admission. The leucocytes were 10,400. His temperature varied from 103° to 104.5°. He showed features of marked toxæmia. The abdomen was soft and was not tender during this time.

On Nov. 15th about 9 P. M. the patient passed a stool, containing about 200 cc. of blood. Before the bowels moved he complained of some pain which disappeared after the movement.

At 10.30 P. M. he again complained of severe abdominal pain with which he cried out and groaned frequently. Soon the bowels moved again and the pain at once ceased. This was a small fluid stool containing perhaps 25 cc. of blood.

At 10.45 P. M. when seen he was very dull and drowsy; the expression was anxious; no complaint was made of pain. The respirations were 30 and the pulse 112 to the minute, both slightly increased over their previous rate. The abdomen was flat, almost scaphoid; the respiratory movements were slight. There was absolutely no tenderness anywhere and no rigidity or muscle spasm. The leucocytes were 7500 per cmm. The temperature had been 103.7° at 8 P. M. It fell to 101.3° at 9 P. M. when the blood was passed and then rose to 105.8° at midnight.

The possibility of perforation was discussed but as it did not seem probable, morphia, gr. ⅙, was given hypodermically. During the night between the 15th and 16th the patient had three stools, all of which contained some blood. With each he complained of pain and had some hiccough, but did not vomit. The leucocytes at 12.30 A. M. on the 16th were 8900, and at 8.30 A. M. were 15,800.

The following note was made by Dr. Futcher at 11 A. M. "The patient is very dull and drowsy; there is decided pallor of the face; some twitching of the hands. No complaint is made of pain. The abdomen is not distended; respiratory movements are seen throughout but are slightly diminished below the umbilicus. The patient winces on pressure. There is slight tenderness in the right lower quadrant and slight muscular rigidity, but no muscle spasm. The hepatic flatness which reached to the costal margin in the right nipple

line at 11 P. M. last night is now 8.5 cm. above the costal margin. In the mid-axillary line there is no obliteration of the hepatic flatness."

At 12.15 noon the hæmoglobin was 80 per cent, the red cells 5.900,000, and the leucocytes, 17,500. At 3 P. M. the leucocytes were 15,400.

The patient was seen by Dr. Osler at 6 P. M. and it was noted that "the pulse was of fair volume, the abdomen not distended, and showing fair movement on respiration. There was no liver dulness in the right nipple line."

At 7 P. M. the leucocytes were 14,000. At 8 P. M. the condition had changed markedly since the note made at 6 P. M. Dr. Futcher noted that "the abdomen is distintctly distended, the respiratory movements are absent, there is marked rigidity and muscle spasm on both sides. There is no liver dulness in the right nipple line. The patient complains of some pain and there is marked tenderness on palpation. There is some hiccoughing at times but no vomiting. The pulse is 144, much smaller and weaker."

A surgical cosultation was held and operation decided on. At this time the diagnosis of peritonitis was evident. About 10.15 P. M. he vomited some greenish fluid. At the same time he passed about 400 cc. of blood from the bowel. The leucocytes were 16,000.

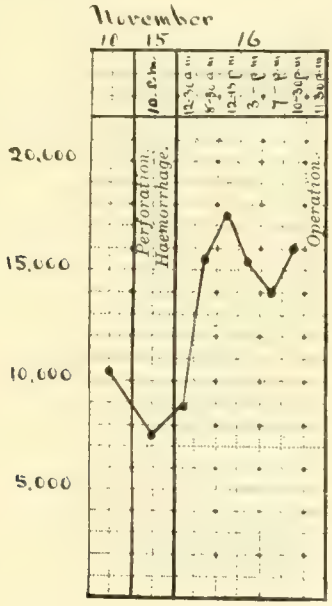
Operation was done by Dr. Finney. It was done without much hope of recovery. Under cocaine the abdomen was opened. Gas escaped from the peritoneum. The cavity contained a considerable amount of bloody exudate with fæcal matter in the pelvis. Coverslips from the exudate showed streptococci. About 12 cm. from the ileo-cæcal valve was a large gangrenous area in which were two perforations. An attempt was made to close these, but the stitches tore through the friable bowel wall and none could be made to hold. The patient's condition rapidly became worse; it was evidently impossible to close the perforations, and the operation was discontinued. The patient died very shortly afterward, about midnight. The lower end of the ileum when examined after death was found to be practically one large ulcer with the walls so thin that they rapidly tore.

Remarks.—It is to be kept in mind that everyone seeing this case had in view the possibility of perforation from the onset of the symptoms. On the evening of Nov. 15 this was discussed and morphia only given after its probability seemed unlikely at that time. There were two points which led us astray—first, the onset of symptoms with hæmorrhage; and second, the absence of any marked abdominal signs, until 8 P. M. on Nov. 16.

There were two points which should have set us right earlier had we given them enough consideration. One was the blood count, which on admission was 6,080,000 red cells with 84 per cent of

hæmoglobin. On Nov. 16 after the hæmorrhage the only change was a drop in the reds to 5,900,000 and the hæmoglobin to 80 per cent. At the same time there was so much shock, if one may so term the condition, that our suspicions should have been strengthened and a further cause than the hæmorrhage looked for. The second point was the marked sudden decrease in liver dulness with a *much retracted abdomen.* This should have been considered more than it was.

CASE XVII. LEUCOCYTE CHART.



The case also illustrates a cycle of events described by some writers, namely a period of collapse followed by a time of improvement. About noon on Nov. 16 the condition was much better than it had been earlier in the day. This was attributed to recovery from the haemorrhage. The fact that he was given some morphia after the onset may have influenced the abdominal symptoms somewhat. To note some of the features in detail:

Onset.—This was about 9 P. M. on the 15th and was probably with some pain and the passage of the bloody stool. The pain was severe a short time later and came on in paroxysms.

Facies showed no special change. From admission the patient had a pinched, anxious expression.

Hiccough.—This only came on during the night of the 15th and then usually with the movements of the bowels.

Vomiting.—This only came on late on the 16th.

Respirations.—These were slightly increased but showed no marked increase.

Pulse.—This increased from about 96 to 120 within a few hours after the onset.

Abdomen.—There was retraction until late on the 16th. The respiratory movements were present throughout until late on the 16th with the onset of general abdominal features. Rigidity was not marked, but although slight, should have drawn special attention when occurring in a retracted abdomen. Muscle spasm came on late.

Liver dulness, as already noted, was early diminished markedly. Percussion and auscultatory percussion were practically of little service.

Leucocytes.—These were as noted from 7500 at onset to 14,000 to 17,500 during the 16th.

CASE XVIII.—*Typhoid fever; perforation of ileum on 13th day; general peritonitis; death; autopsy.*

W. B. (Medical No. 13857), black, male, aged 19, was admitted to the medical service Dec. 30, 1901 on the sixth day of his illness. His temperature was 102°, rising to 104.6°. He complained of stiff neck and headache.

The present illness began with headache, stiffness in the neck, dull feelings, no nausea or vomiting, nose bleed, slight cough, no night sweats. He worked until three days before admission when the pain in his neck became so severe that he went to bed. On the morning of admission he spat up a small clot of blood and blood-streaked sputum. The leucocytes were 11,600.

Dec. 31, Dr. Cole.—The patient is in good condition. There is no stiffness of the neck; no glandular enlargement. The lungs show coarse râles on auscultation. The pulse is 120 and regular; temperature, 104.6°; respirations, 24. The abdomen is full and distended; respiratory movements present. He complains of pain and tenderness about the umbilicus and right iliac fossa. Liver dulness begins at the 6th rib, and extends to the 7th. The Widal reaction is positive.

Jan. 1, Dr. Osler.—The abdomen is held rigidly and is somewhat tender.

Jan. 2, 1902.—The temperature has ranged near 104°. Sponges have

had little effect. The abdomen is somewhat distended still. The spleen is not felt. The pulse is 140. The patient is rational; has had no delirium; has been nauseated several times and has vomited. There has been muco-purulent, blood-tinged sputum.

Jan. 4, Dr. Cole.—The patient's temperature continues high; pulse smaller and weaker, 136; no delirium; looks dull and stupid. The abdominal walls are held stiffly. He complains a good deal of tenderness in the right iliac fossa; no pain. The abdomen is everywhere tympanitic. Leucocytes, 17,300.

Jan. 5.—While the patient was in the tub, at 5.30 this morning, he complained of severe abdominal pain. At 7.45 A. M. he was complaining of pain in the right iliac fossa. Respiratory movements were present. The abdomen was distended, tympanitic, fairly soft on palpation. He complains of great tenderness on pressure in both iliac fossæ, especially the right. No liver dulness is made out. His general condition is about the same. Many piping and sonorous râles are heard over both backs. Leucocytes, 14,000.

10 A. M.—He complains of abdominal pain. The abdomen is symmetrical, a little full; the walls held stiffly; no muscle spasm; tenderness on deep pressure. Liver dulness extends to nearly within 6 cm. of the costal margin. The pulse is of small volume and low tension. The sputum is blood-tinged.

Jan. 6, 1902, Dr. Cole.—Liver dulness is 5 cm. above the costal margin. The abdomen is distended and tympanitic; no muscle spasm; walls held firmly; no pain or tenderness. The temperature is higher, reaching 105.6° this morning. Leucocytes, 16,000.

Jan. 7, Dr. Cole.—The temperature has been continuously elevated; no delirium; some muscular twitching. The pulse is small and weak. The patient last night complained of abdominal pain and is still complaining of pain just to the right of the umbilicus. The respiratory movements are fairly good. The abdominal walls are rigid, more so than at any previous time, relaxing slightly on steady palpation. He complains of considerable pain throughout the abdomen, slightly more on the right side. No movable dulness is made out. Hepatic dulness is 6 cm. from the costal margin. There is some retching, but no vomiting.

11 A. M.—Leucocytes, 10,000.

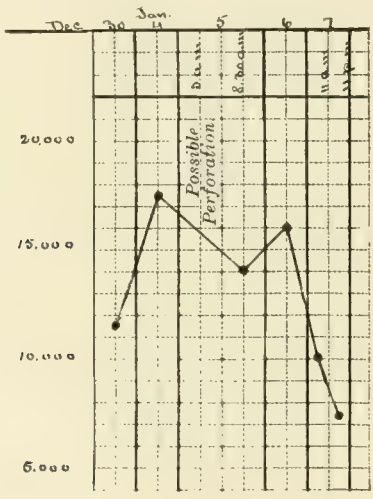
Jan. 7, 9.30 P. M., Dr. McCrae.—His general condition is worse. He is irrational and complains at times of severe abdominal pain, with which he cries out. The pulse is 152, of small volume and regular; respirations, 36. Coarse, high-pitched râles are heard over the left axilla. The abdomen is symmetrical but is more distended than this morning; respiratory movements almost absent below the navel. There is everywhere resistance to palpation, the muscles being very tense. Palpation is almost negative, both sides seeming the same. Pain was complained of everywhere on deep palpation. Liver dulness is present in the mid-axillary line only.

11 P. M.—Leucocytes, 7300.

Jan. 8, 1 A. M., *Surgical consultation* (Dr. Mitchell).—The patient is lying on his back crying out with pain, irrational, rigid throughout. His neck is extremely stiff. He cries out when any attempt is made to flex it. There is ankle-clonus on both sides. The pulse is extremely rapid and weak. The abdomen is boardlike and rigid. It is impossible to make out anything as to his condition. He is evidently in extremis. Operation is not advised on account of the very weak and hopeless condition of the patient. There is a possibliity of a general peritonitis or of meningitis.

Lumbar puncture was done and 20 cc. of clear limpid fluid withdrawn. This was not under pressure.

CASE XVIII. Leucocyte Chart.



4.15 A. M.—His general condition is evidently worse. The abdomen is not so boardlike. There is not so much pain. He has had two stools since 1 A. M. The pulse is running, impossible to count. There has been delirium since 4 A. M., with shouting and struggling.

7.45.—He vomited brownish material, partly through nose, and dropped back dead.

Autopsy.—Typhoid fever. Hyperplasia of mesenteric lymph glands. Ulceration of Peyer's patches in ileum; perforation. General fibrinous, purulent peritonitis. Acute splenic tumor. Swelling of liver and kidneys. Broncho-pneumonia. Purulent bronchitis.

Bacteriological notes.—Cultures from the cerebro-spinal fluid were negative.

Remarks.—It is difficult to say when the perforation occurred, although possibly on the morning of the 5th. It has been noted that the abdominal symptoms were marked throughout his illness. He had cried out with pain and with complaints of various kinds. He was always a difficult patient from whom to get a satisfactory answer. When seen by Dr. McCrae on Jan. 7 for the first time, there did not seem to be anything especially suggestive about the abdominal condition. There was marked complaint of pain throughout his illness. The leucocytosis and varying abdominal signs all contributed to the non-recognition of the condition, although its possibility was ever in mind. It is interesting to note that with the general peritonitis and perforation, the bowels moved and the patient passed gas by rectum very frequently.

Discussion of the perforation cases.

Probably the best idea of the picture presented by cases of perforation can be obtained by a consideration of the symptoms in detail. We may again draw attention to a point strongly emphasized by Cushing (9), Shattuck, Warren and Cobb (10) and others—namely that a distinction is to be made between the symptoms of perforation and those of the resulting more or less general peritonitis. The usual text-book description is more of the symptoms of the latter condition. As long as the operation is delayed until this last stage there can be little hope for decrease in our mortality.

Symptoms before perforation.—These, which by some writers are considered to be warnings—and therefore by inference of some help—have in some cases only served to confuse and render the diagnosis more difficult. Of course, all cases with suspicious symptoms should be carefully watched and any increase in the abdominal features should call for surgical consultation, as has been emphasized in the remarks of Dr. Osler previously quoted. Yet we can not but feel that in many of our cases the sudden onset has been the most valuable help in diagnosis. In a patient who has been having abdominal symptoms for some days, the onset of perforation, as we have learned, may mean little change and only the development of extensive peritonitis may be recognized. Also when we consider the number of patients with suspicious abdominal symptoms, such as pain and tenderness, perhaps associated

with leucocytosis (as discussed in Group e) that afterward clear up completely, we cannot fail to attach less importance as an aid to diagnosis to the so-called warning symptoms and pre-perforative leucocytosis. Such symptoms occur so often unassociated with perforation, that they can not be considered as even a frequent sign of impending perforation, but should nevertheless act as a stimulus to the most careful, frequent and thorough observation by both physician and surgeon. It must be remembered that probably only hourly counts of the leucocytes can be of much service in detecting a perforative leucocytosis and as we have seen in many cases the perforation may occur in patients whose previous condition has not indicated the necessity of such counts. Four cases of this series of eight presented no abdominal features before perforation. Three patients had distention, rigidity and abdominal pain, in two of these accompanied by leucocytosis. In one case there was intestinal hæmorrhage one day before the perforation.

Onset.—One feature stands out in all but one of the cases, namely the suddenness of onset with pain. In the eighth case there was pain throughout the attack and the time of perforation could not be fixed. The patients usually cried out with the pain, so as to attract the attention of the nurse or attendants. In two this occurred during a tub-bath, in one while on the bed-pan. The pain is usually severe and referred to various regions, most often to the lower abdomen and the umbilical region. In two instances it began in the penis and extended into the abdomen; in one case it was localized about McBurney's point. In two patients the pain and perforation were accompanied by hæmorrhage from the bowels. Chill at onset was observed in one case, in which perforation occurred with intestinal hæmorrhage. Sweating was twice noted, both times profuse. An immediate increase in the pulse rate was not common; it was seen in two, in one of which it was accompanied by immediate increase in the respiration (in this case there was also chill, sweating and hæmorrhage at the time of perforation).

It is to be noted that in only one case was there any drop in temperature at onset and this of between two and three degrees and immediately followed by elevation; and that in six there was *immediate elevation* after the onset.

Time of perforation.—The earliest was on the eleventh day of

the disease and the latest on the thirtieth. The others occurred on the twelfth, fifteenth, sixteenth (two), eighteenth and twenty-fifth.

Symptoms after perforation.—These depend upon or are influenced by various factors, firstly, the position of the perforation; secondly, the organisms escaping into the peritoneal cavity; and thirdly, the general condition of the patient, all of which influence the rapidity of the spread of peritonitis and the symptoms presented. It is convenient to consider the symptoms under two heads—first, general symptoms, and second, local abdominal symptoms. While in some cases which have gone for a long time after perforation the symptoms can be divided into two periods, those we wish to consider most carefully are the earlier ones. The later condition, in which the symptoms are due to more or less extensive peritonitis, is generally easily detected and if possible is to be avoided by operating before it has developed. In certain cases the earlier stage is overlooked. The symptoms in Cases XI to XV occurred during the period of three and a half to thirteen hours. In the remaining three the time was over twenty-four hours. In two of these the presence of intestinal hæmorrhage was a confusing feature and the remaining case was not operated upon.

General Symptoms.

Facies and general appearance.—The facial appearance was practically normal in four cases throughout, a fifth showing a pinched expression only after some hours. In one there was the "risus sardonicus," and in two there was a distressed anxious look.

The *decubitus* was dorsal in six throughout, three of these lying with the knees drawn up. In two the decubitus was right lateral with the knees drawn up.

Sweating was observed in three cases.

Collapse was present only twice, both times in association with hæmorrhage.

Temperature.—In only one case was there no change in the temperature. In seven there was slight elevation following the perforation, and this in six instances was followed by a fall in temperature which in one case reached normal. This was a case in which hæmorrhage accompanied the perforation.

Pulse.—The rate showed practically no change in two instances.

In six the rate increased, two suddenly and four gradually. As a rule the quality of the pulse becomes poorer as the symptoms progress but this is not certain enough to be of value.

Respirations were unchanged in three cases. Of five showing increase in the rate, three rose gradually and two increased at once. In two there was a subsequent drop, both being cases of associated hæmorrhage which had received opium.

Hiccough occurred in three, in two of which it was a rather late symptom.

Nausea and vomiting were observed in only one instance and then rather late.

Bowels.—There are notes of the bowels moving in five cases after the perforation, one of these being a case of general peritonitis. In two cases the stools contained large amounts of blood and in one there was diarrhœa with pain. Three patients expelled flatus after perforation.

Leucocytes.—In three cases there was practically no change in the leucocytes after perforation. In one of these the leucocytes were normal throughout and in the remaining two there had been leucocytosis previous to the perforation, which did not change appreciably. In five cases the leucocytes rose in varying degree after perforation. It is significant that the two cases showing the greatest rise in leucocytosis after perforation were those in which hæmorrhage and perforation coexisted. The leucocytes in these instances were 14,000 and 17,500. In the remaining three cases the highest leucocyte counts were between 8000 and 12,000.

Local Abdominal Features.

Pain was a prominent symptom in seven of the eight cases. In the eighth it was severe at the onset but disappeared after the administration of opium. In five cases it occurred in intense paroxysms while in two it was constant and varied but little in degree. It was referred to the right iliac fossa by four, the right hypogastrium by two, by one to the umbilicus, and in the last case it was general.

Appearance of Abdomen.—The abdomen was natural and without distention in three instances, in one of which there was retraction of the walls. In a fourth there was no distention except of the lower abdomen by a myoma of the uterus. The abdomen

showed distention in four, in all of which it had been present before perforation. In one instance the distention remained unchanged as the symptoms progressed. In one it increased greatly and in another it decreased after movement of the bowels, while in a fourth it varied in amount.

Respiratory Movements.—There was no case which showed immediate diminution of the abdominal respiratory movements. In four cases they were well marked throughout. In three they were diminished in two, six, and twenty-four hours respectively after perforation. In one case there was diminution below the navel due to a myoma.

Rigidity was present in some degree in all, being greater on the right side in three and fairly general in three. In one it appeared only as a late symptom.

Muscle Spasm was never a very early symptom, the earliest time at which it was detected being about five hours after the perforation. In two cases there was none noted.

Tenderness on palpation was usually an early and striking sign, and often varied in degree. In four instances it was fairly general, and in three of these rather more on the right side. The point of greatest tenderness was definitely located in the right iliac fossa in three; in the hypogastrium in one, and in two it varied in position.

Liver Dulness was not diminished in two cases, while in two it had been diminished before the perforation and was practically unchanged afterwards. Of four cases in which the liver dulness was decreased it occurred in two with a flat abdomen, and in another without any increase in the previous distention, while in the fourth it was associated with distention.

Dulness in the flanks was made out in five cases, in two of which it was definitely movable.

Auscultatory percussion was of no value in three cases in which it was tried.

Rectal examination was also negative except for slight tenderness in one case.

There is one condition sometimes associated with perforation to which we would draw special attention, namely hæmorrhage, as shown in Cases XVI and XVII. Of the seven cases of perforation here reported, the complication was recognized within nine hours

in five, but in the two with hæmorrhage not until after twenty-four hours had passed. The combination is not rare; among the 34 cases of perforation in the medical service of this hospital, in 7 has hæmorrhage occurred at the same time. It may be added that in none of these was the perforation recognized early. The symptoms were always attributed at first to the hæmorrhage. This would seem to be worthy of consideration as a contra-indication to the use of opium for hæmorrhage; certainly one would say until the possibility of perforation has been excluded. But who can do this with certainty? We thought we had done it in Case XVI, but we were wrong. The same may be said of Case XVII, where everyone seeing the case had perforation in mind as a possibility throughout. It may be necessary to quiet a restless patient having hæmorrhage, but a small dose of morphia hypodermically will do this and is to be preferred to opium by the mouth or bowel, the effect of which will probably last much longer.

The diagnosis of perforation.—One has only to see a few cases of perforation or study their histories to appreciate the fact that there is no regularity in the symptoms and that no symptom or group of symptoms is pathognomonic. The classical description of the symptoms is not so much of perforation, as of the resulting changes. Not all cases are difficult. Between a case such as No. XV of this series where the diagnosis was made at once on the first examination to one where not a suspicion is entertained until the autopsy shows general peritonitis, there are all grades and variations. Any case of typhoid fever may perforate. It may be said that preparations for the diagnosis should be made long before the perforation occurs. Much in its recognition depends upon seeing the patient at the onset of symptoms. The nurses and attendants must be carefully instructed to report at once any suspicious symptoms. The importance of this has been emphasized by Dr. Osler. (1) Abdominal pain, any sudden general change, alterations in the pulse and respiration, etc., should be reported at once. The house physician should never disregard such warnings, but see the patient immediately. He may be frequently called for conditions of no moment, but he must not let this render him careless. There should also be careful study and noting of the patient's condition every day. These notes should be on paper and not left to the physician's memory. A careful description of the previous general

state, and especially the abdominal condition, should be available in the event of complications later in the disease. With the appearance of any suspicious signs, of course constant observation is most essential. The patient should be seen every hour and accurate notes written out. Along with this should go a surgical consultation. The surgeon, who has seen the case from the onset of abdominal symptoms, is in a much better position to advise for or against operation. It is well for the surgeon to familiarize himself with the ordinary abdominal conditions in typhoid fever, some of which so closely simulate perforation. So great is the variation in the symptoms that no satisfactory general description can be given, nor is it well that it should be attempted. Those handling typhoid fever patients have to realize that perforation comes under many guises and that to attempt its recognition from any constant combination of signs is hopeless. No symptom is constantly present and no significance should be attributed to the absence of any one. There are, however, certain points which stand out, and of these a most important one is the onset. This is usually sudden and with pain. Such an occurrence should excite suspicion. In the cases which have had pain for days before the perforation, there may be an exacerbation of the pain which attracts attention, or there may be nothing more striking than before. Other symptoms may accompany the pain, such as nausea or vomiting, sweating, rise in pulse rate, etc., but the pain is by far the most constant feature. Other conditions causing abdominal pain have always to be most carefully excluded. These are many and have been considered by one of us in another article. (11) After the onset we should say the most constant features are pain, often in severe paroxysms, tenderness, and some rigidity. Others may be present, such as vomiting, sweating, change in temperature, pulse and respiration, impairment of abdominal respiratory movements, muscle spasm, decrease in the area of liver dulness (which is only of value if one has careful notes as to its extent previously and is of little importance where there is marked abdominal distention), movable dulness in the flanks, leucocytosis, etc. But from the absence of any of these no conclusion should be drawn. Their occurrence is important, their absence is not.

We speak here of the early hours after perforation; later these features may all be present. Compare also the symptoms in the group below where perforation was suspected and the difficulties of

diagnosis are more evident; pain, tenderness, rigidity, leucocytosis, changes in pulse, respiration, and temperature may all be found without perforation. The difficulties are evident. Have we any other means of making the diagnosis? The only one of value is exploration. This should be done under cocaine and is practically without danger. Certainly it is better to take this slight risk than to let a doubtful case go beyond the limit of recovery. In other doubtful conditions of the abdomen we are accustomed to advise exploration as a diagnostic measure considering the risk less from operation than from delay. The suspicious typhoid case is analogous except that here the delay of an hour corresponds to that of a month in an advancing chronic case. We may say here as of appendicitis that while exploration is often too late, we have never regretted its being done too early. That all suspicious cases do not require exploration is shown by the group given subsequently. In some of these we waited from hour to hour, ready to operate at once should any advance in symptoms be noted. A positive diagnosis of perforation always before operation is not to be expected nor is it wise that it should be demanded. What we have to decide is whether the condition is of sufficient gravity to warrant an exploratory operation to render certain the existence or not of some abdominal complication.

Time of Operation.

The shortest time elapsing between perforation and operation in the seven cases was three and a half hours. The two cases in which operation was longest delayed—25 and 26 hours—were both accompanied by hæmorrhage. In one case operated upon 13 hours after the perforation, some delay was due to a long operation on an emergency case occupying the surgeon. The remaining three cases were operated upon respectively $7\frac{1}{4}$, 8 and 9 hours after perforation. The following table shows the relation between the time of operation, the leucocytosis, the bacteriological findings, and the result.

Case.	Hours.	Leuc.	Result.	Bacteriology.
XI	13	7,500	Recovery.	B. coli com., B. proteus vulgaris, unidentified bacilli.
XII	9	5,000	Death, 63 hrs.	Strep. pyog. Typho-colon B.
XIII	$7\frac{1}{4}$	11,500	Recovery.	Cultures negative.
XIV	8	12,500	Death, 7 days.	Bac. coli com.
XV	$3\frac{1}{2}$	15,800	" 12 hrs.	Bac. coli com.
XVI	26	14,600	" 22 "	Bac. coli com. Staph. pyog. aureus.
XVII	25	17,500	" 1 "	Streptococcus pyog.

Operation.

Anæsthetic.—In the first three cases cocaine was used in the beginning of the operation with whiffs of chloroform after the peritoneum was opened. In the last four cases cocaine alone was used. As is brought out by Cushing (12) the successful use of cocaine depends largely upon experience.

Incision.—The incision of choice is through the right rectus muscle, separating the fibres. This we have used in three cases. Three times the incision of Lennander at the outer border of the right rectus was used, and in one case an incision at the inner border of the same muscle. The lateral incisions are much to be preferred, giving the best exposure of the ileocæcal region, and offering the most favorable conditions for drainage.

Condition of peritoneum.—In three cases on opening the abdomen there was an escape of gas and in four there were fæces in the peritoneal cavity. There was usually a considerable amount of free fluid, always turbid, and in five cases definitely purulent. In one ($3\frac{1}{2}$ hours after perforation) the fluid was of very small amount and confined to the immediate neighborhood of the perforation. Peritonitis was twice limited and five times extensive. Of the cases which recovered there was in one limited, in the other extensive peritonitis. The mesenteric glands were usually enlarged.

Intestines were distended in four cases, two of which recovered.

Perforation.—In only one case was there more than one perforation. All were in the ileum and varied in position from ten to forty-five centimetres from the cæcum. The size of the perforation was from two millimetres to a centimetre in diameter. They were usually clean cut and situated in the centre of a Peyer's patch.

Operative procedures.—In one case only were we unable to close the perforation on account of the friability of the surrounding bowel wall. The perforation has otherwise been closed by a purse string suture of fine silk, reinforced by one or two Halsted mattress sutures. Any suspicious-looking Peyer's patches may be turned in by the same method. We have never had such a suture fail to remain secure and at autopsies on the fatal cases we have always found the suture intact, even in the presence of general peritonitis.

Irrigation has been used in only one case where there was very extensive if not general peritonitis at the time of operation, the patient dying immediately afterwards. We prefer to thoroughly wipe away the exudate with gauze pads moistened with normal salt solution. Great care is taken to keep the intestines within the abdominal cavity during this cleansing, and so avoid the shock of evisceration. The search for the perforation should be systematic, beginning at the cæcum as a land-mark and following the ileum upwards. Much time may thus be saved and the surface of the bowel cleansed as examined. With a little experience on the part of the operator there need be little pain causd by these manipulations. The parietal peritoneum being more sensitive should be avoided as much as possible.

Closure.—The omentum is pulled down over the point of suture and over any suspicious ulcers as an extra protection and the region is drained with iodoform gauze and protective wicks. In no case have we closed the wound without drainage.

Immediate effects of operation.—In one case death immediately followed the operation, the patient being almost moribund when placed on the table, suffering from the combination of perforation and intestinal hæmorrhage. In three cases the condition was practically unchanged and three others showed almost immediate improvement.

Subsequent course.—In those cases which recovered the course of the typhoid fever was milder after the operation. One of these (Case XI) ran a short and uneventful convalescence. The second (Case XIII) developed bronchitis and from constant straining the small intestine was pushed out through the wound on the sixth day. It was cleansed and replaced. Subsequently convalescence was slow and there was a mild nephritis. The patient left the hospital well. Intestinal obstruction from adhesions and extensive peritonitis resulted fatally on the third day in one instance (Case XII).

Ultimate results.—Two patients eventually recovered. One lived a week and died from profound toxæmia. Case XVII died one hour after operation; Case XV, 12 hours; Case XVI, 22 hours and Case XII, 63 hours.

Bacteriology and Autopsies.—The bacteriological and autopsy findings are given in detail with the histories above.

As would naturally be supposed, the organisms obtained from the peritoneal cavity are a good index to the prognosis, those cases with the least virulent organisms liberated having the best chances for recovery. Autopsies were obtained in three cases in all of which the diagnosis of typhoid fever was substantiated.

(d) *Suspected Perforation.—Operation.*

Of two cases explored on account of symptoms suggesting perforation one showed a mild grade of peritonitis, which cleared up after the operation, while in the other the symptoms were caused by intestinal hæmorrhage. In the first case the fever ran a much milder course after the operation and the whole trend of the symptoms was toward improvement. The patient recovered and left the hospital in the seventh week. It is an important case as showing that a cocaine exploration may have no injurious effect and here even seemed to have a beneficial influence on the typhoidal process. It is natural that one should not wish to operate unnecessarily. When in doubt, however, and perforation is strongly suspected, it is certainly much wiser to subject the patient to an operation, which is in itself harmless, than by waiting for positive signs to allow an extensive peritonitis to develop and so practically take away the patient's chances for recovery.

In the second case of this series, the symptoms were evidently due to intestinal hæmorrhage. The patient's condition, which was desperate, was not affected by the operation and she died of hæmorrhage and toxæmia.

Case XIX.—*Typhoid fever; abdominal symptoms; operation; mild peritonitis; no perforation; recovery.*

H. H. (Medical No. 12077, Surg. No. 11113), male, black, aged 22, was admitted to the medical service on Oct. 26, 1900, apparently in the third week of typhoid fever. The Widal reaction was suggestive on the day after admission. The patient was in good condition at the time of admission; temperature 100°, rapidly rising to 105° in the afternoon; to 105.2° on the following day; pulse 104; respirations 20.

The abdomen on admission was natural, not distended; no tenderness. The spleen was palpable. Liver dulness reached the costal margin in the mammillary line.

Oct. 28, 12.15 A. M., Dr. Futcher.—About 8 P. M., just after a tub-bath, the patient suddenly cried out with abdominal pain, which he stated was on the left side of the abdomen in the lumbar region near

the ribs. It lasted 10 or 15 minutes and disappeared, and four hours later had not returned. There was no nausea or vomiting. At present he is quite comfortable, lying flat on his back with both knees flexed. His temperature at 8 P. M. was 104°; at 10 P. M., 103.2°; at 12, 102.2°; pulse rather small and easily compressed. The abdomen is not distended; respiratory movements well seen above the umbilicus, slightly limited below. The abdominal muscles are held rigidly and contracted with no apparent difference in the two sides and no actual muscle spasm. The patient complains of slight sensitiveness in the lower left quadrant. The liver dulness reaches the costal margin. The percussion note is everywhere tympanitic. There is no movable dulness. The facies is natural; hands and feet slightly cold and moist. Leucocytes at 10 o'clock, 10,500; at 12 o'clock, 13,000.

2.15 A. M., Dr. Futcher.—The patient is comfortable. The abdomen is a trifle more distended, the liver dulness now extending nearly to the middle of the 6th interspace, 3 fingers breadth above the costal margin. Muscle rigidity is still marked over the abdomen. Deep palpation causes some pain in the lower left half of the umbilical region. The pulse is 96; respiration 26.

Surgical consultation.—Dr. Mitchell, 2.30 A. M., Oct. 28, 1900. Exploration is advised.

Operation.—Oct. 28, 1900, 3.30 A. M., Mitchell, Cocaine. Exploratory laparotomy; free fluid in peritoneal cavity; no perforation; closure with silver.

The patient was given ⅙ gr. of morphia, hypodermically, in the ward and ⅛ gr. just before the operation. An incision was made at the inner border of the right rectus muscle, and the muscle retracted to the median side. A small amount of slightly cloudy fluid was found in the peritoneal cavity. The ileum was distended in its lower part, collapsed in its upper. Swollen Peyer's patches were prominent in the lower part of the ileum. One of these, 15 to 20 cm. from the ileum, was peculiar, being hard, dark red in color, with soft white areas through it. The peritoneum over it was dull and opaque. The blood vessels were much distended. The lymphatics were not visible. The Peyer's patch itself was about 1½ cm. in diameter. The mesenteric glands were much enlarged. There was general distention of the blood vessels over the distended ileum. There was no perforation. The fluid was wiped out and the omentum was pulled down over the suspicious looking ulcers. The wound was closed with silver. The patient stood the operation well, and slept and snored through a great part of it. Handling of the distended ileum was painful. There was no change in the pulse.

Oct. 28, 4 P. M.—The patient has been comfortable since the operation, complaining of no abdominal pain. His temperature after the operation was 104° and has fallen this morning to 102.2°. His pulse is good. Leucocytes, 6000.

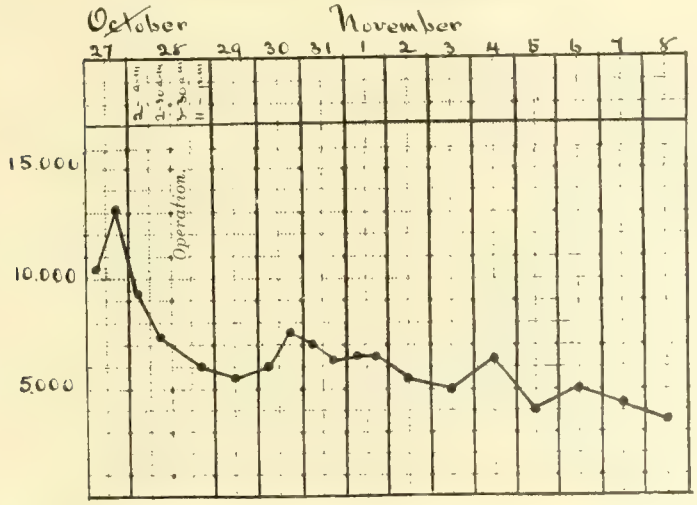
Oct. 31.—The temperature has remained elevated, ranging from 103° to 104°. There are no abdominal symptoms.

Nov. 5.—The wound has healed per primam. The temperature has gradually fallen. The general condition is excellent.

Dec. 6.—He is discharged well.

Bacteriological notes.—Coverslips from the fluid in the peritoneal cavity showed bacilli and a few cocci. Cultures were negative.

CASE XIX. LEUCOCYTE CHART.



Remarks.—The character of the pain coming on suddenly at the time of the tub, the rigidity of the abdominal muscles, the tenderness in the abdomen, which had not been present previously, the rise in leucocytes, all seemed to justify an abdominal exploration. The course of the typhoid fever was certainly much milder after the operation. The general trend of his symptoms following operation was towards improvement. The fluid in the peritoneal cavity containing bacilli and cocci evidently indicated a low grade of peritonitis, which seems to have been relieved by the operation. This case is of special interest as an example of peritonitis without any perforation. It is the first one that has been recognized in this hospital. How far such a condition may explain abdominal symptoms such as are shown by the patients in the next group is a difficult question to answer.

Case XX.—*Typhoid fever; hæmatemesis; intestinal hæmorrhage; abdominal symptoms; operation; no perforation; death; autopsy.*

P. R. (Medical No. 12350), female, black, aged 10, was admitted to the medical service Dec. 31, 1900, on the eighth day of typhoid fever. The temperature on admission was 104.5°, rising in the afternoon to 106°; pulse 120; respirations 40. The Widal reaction was positive on the day after admission. On admission the patient was dull and looked ill. The lungs were negative. The abdomen was much distended; everywhere tympanitic; no rigidity; no tenderness. The spleen was not felt. Hepatic dulness reached the costal margin in the mammillary line.

Jan. 1, 1901, Dr. McCrae.—The abdomen is everywhere soft with no tenderness. The temperature is running high, but responds well to tubs. The pulse is rapid, 152, though of fair volume.

Jan. 4.—During the last 24 hours the patient has passed two stools tinged with blood after enemata. The child is quiet and not complaining of any pain.

Jan. 5, Dr. McCrae.—At 4.10 P. M. the patient vomited 40 cc. of fluid, containing from 10 to 15 cc. of bright red blood. She was seen a few minutes later and was found on the right side with her knees drawn up. She was quiet but when questioned complained of abdominal pain. At times she wrinkled her forehead as if in pain. She objected to having her legs straightened, or being turned on her back, crying out with pain when disturbed. The pulse is 168 and of small volume. The abdomen is natural; respiratory movements well marked. She points to the navel when asked for the seat of pain. There is no tenderness, rigidity or muscle spasm. Liver dulness begins at the 6th rib, and extends to the costal margin. There is occasional coughing, during which the child moans with pain.

Jan. 5, 8 P. M., Dr. Futcher.—She has had less abdominal pain during the last hour and a half and no more vomiting. The pulse is 160; respirations 40. The abdomen is a trifle fuller. Respiratory movements are still free, although slightly limited below the umbilicus. There is considerable tenderness in the right hypochondriac region. There is a peculiar suggestive retraction of the upper lip and occasional peculiar sighing respirations. The hepatic dulness now reaches 1.4 cm. above the costal margin in the mammillary line. There is absolutely no rigidity or muscle spasm.

Surgical consultation, Jan. 5, 11 P. M., Dr. Mitchell.—The present indications are not for exploration. There is probably gastric ulceration but not perforation or peritonitis. It is decided best to watch carefully.

11.30 P. M.—There is little change in patient's condition, excepting that she is a trifle weaker. There is a possibility of the condition being due to intestinaal hæmorrhage. The pulse is 160.

Jan. 6, 6 A. M., Dr. Futcher.—There has been some abdominal pain

since the last note. The hæmoglobin is 45 per cent. Two days ago it was 70 per cent. The probability of a hæmorrhage is strengthened by this drop. Quite marked tenderness is elicited in the right hypochondriac region; no distention, rigidity, nor muscle spasm. Favoring perforation are the following points: The sudden onset of pain, vomiting, abdominal tenderness and rapid pulse. There is considerable doubt as to the diagnosis, hæmorrhage being the greatest probability. The patient is to be given the benefit of the doubt and an exploratory operation done.

Operation.—Jan. 6, 1901; Mitchell; cocaine. Exploratory laparotomy; no fluid in the peritoneal cavity; no perforation; ulceration of ileum, with blood in the small intestines.

Gall bladder distended and tense. Closure with silver.

The patient was given ⅛ gr. of morphia in the ward, and a second ⅛ gr. at the beginning of the operation. An incision was made through the sheath of the right rectus muscle at its inner border, and the muscle pulled aside. The peritoneal cavity showed no evidence of peritonitis and no free fluid. The large intestine was bluish and evidently contained blood as did also the lower part of the ileum. The lower portion of the ileum was studded with a great number of Peyer's patches, some 2 cm. in diameter, with enlarged vessels about them. The patches farthest from the cæcum showed less reaction, less elevation and thickening. About two or three of the lowermost patches there were areas into which there was extravasation of blood. None of the patches showed any signs of perforation, nor did they present the appearance of pre-perforative ulcers seen in other cases. The appendix was normal. The stomach showed no visible signs of disease and was not distended. The gall bladder was tense and somewhat distended. There was no ulcer which by inspection of the bowel could be fixed upon as the seat of hæmorrhage. The wound was closed with silver. Handling of the viscera was painful at first, causing the patient to cry out. The "moral anæsthetist" was of great assistance during the operation. The patient was told to close her eyes and go to sleep. She complained no more during the operation, although the same handling was repeated, suggesting hypnotism.

Jan. 6, 1901, 11 A. M.—There has been no vomiting since the operation. The patient's condition is comparatively good. She is evidently not suffering from pain. The temperature is 103.7°; respiration, 36; pulse 168.

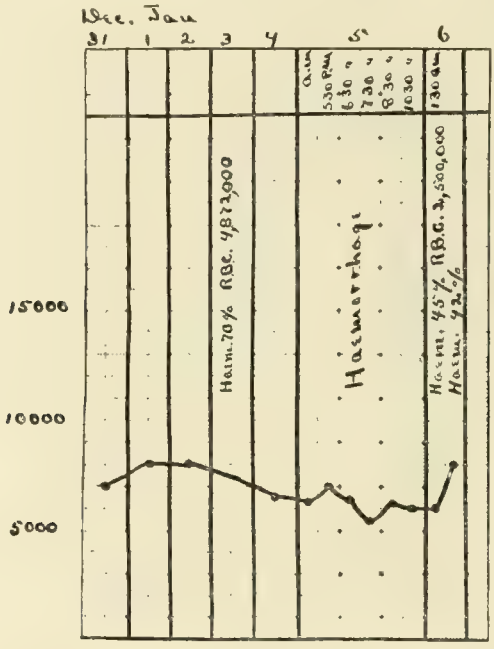
She has not passed any blood by rectum, although the thermometer is blood stained. There is no distention of the abdomen. The walls are quite lax.

Jan. 6, 4 P. M.—The patient's general condition remained about the same until 3.30 P. M. when she vomited. At 3.35 her respirations became suddenly very rapid, shallow, and labored. The child became unconscious. She passed a large amount of thick black fluid by rectum and had a slight general convulsion and died.

Bacteriological notes.—Cultures and coverslips from the peritoneal cavity were negative.

Autopsy.—Anatomical diagnosis: Typhoid fever; swelling and ulceration of Peyer's patches; nodules in ileum and colon; acute splenic tumor; hyperplasia of mesenteric lymph glands; ulceration of gastric mucosa; erosion of artery and hæmorrhage into stomach.

CASE XX. LEUCOCYTE CHART.



Remarks.—This case illustrates the great similarity of the symptoms of perforation and intestinal hæmorrhage; the sudden onset of pain, increase in pulse rate, rapid respiration, vomiting, abdominal tenderness and pain, all suggesting perforation; the rapid, weak pulse, the vomiting of blood, the absence of rigidity and muscle spasm, and the rapid drop in the hæmoglobin favoring the probability of gastro-intestinal hæmorrhage. The leucocytes were of little value, being 7000 on the day of admission, Dec. 31; Jan. 1, 8000; Jan. 2, 8000; Jan. 4, 6600; Jan. 5, at 5 A. M., 6300; at 5.30 P. M., 7000; at 6.30 P. M., 6400; at 7.30 P. M., 5400; at 8.30 P. M., 6200; at 10.30 P. M., 6000; Jan. 6, 1.30 A. M., 6000; Jan. 6, 8000.

It is difficult to estimate the influence the operation had in hastening death. Judging from the patient's condition after the operation and up to a few minutes before death, it would seem that there was no injurious effect directly referable to the operation. She seemed to be doing well up to the onset of the symptoms which immediately preceded death. It was thought possible that the sudden death was due to a fresh hæmorrhage. The absence of blood at the autopsy rendered this improbable. At autopsy it was thought that the hæmorrhage had occurred at the seat of the ulcer in the stomach.

The following case we include with the typhoid group because at the time of admission it was thought probable that the patient was suffering from typhoid fever. The disappearance of symptoms after the administration of quinine, although no malarial parasites were ever demonstrated, suggests the possibility of malaria.

CASE XXI.[1]—*Acute febrile attack with abdominal symptoms; operation, negative findings; recovery after taking quinine; no malarial organisms demonstrated.*

A. B. (Surg. No. 10926), male, black, aged 22, was admitted to the medical service on Sept. 14, 1900, complaining of abdominal pain and headache. He had never had typhoid, malaria or pneumonia. He had drunk ordinary hydrant water and lived in a district in which typhoid and malaria abound.

Present illness.—He has been feeling sick for the past five days, his illness beginning with sharp pain in his left side and shoulder; no chill nor epistaxis; no herpes. On Sept. 10, he gave up work on account of fever and headache. His bowels moved daily. Pain in the abdomen began Sept. 11. His symptoms progressed and grew worse until admission. There has been no nausea nor vomiting.

Admission, Dr. McCrae.—The tongue is lightly coated; respirations, 12; pulse 84, regular. The abdomen is flat; respiratory movements present. The walls are held tightly; no muscle spasm. There is tenderness above the navel, well marked in the hypogastrium and below the right costal margin. The spleen is just felt. The leucocytes are 7400. Liver dulness begins at the 6th interspace and extends about 1½ fingers breadth below the costal margin. The temperature on admission was 102.2°. The Widal reaction was negative.

[1] It is interesting to note that this patient was re-admitted to the hospital on August 25, 1902, with typhoid fever. Typhoid bacilli were obtained in blood cultures. The attack was moderately severe, and for several days he complained of abdominal pain with which he had tenderness and some rigidity.

Sept. 14, 11 P. M., Dr. McCrae.—The patient's condition has been about the same all day. He has been lying on his back with the legs drawn up; respirations varying from 40 to 42; pulse, 84, bounding in character. The abdomen is flat; respiratory movements free. The abdominal walls are tense. There is no muscle spasm, although there is a suggestion of it in the upper right rectus. Tenderness is marked above the navel, very slight below; most marked in the right hypochondrium and right epigastrium.

There is practically no tenderness in the right iliac fossa. The general condition seems worse tonight. He is quiet and not complaining, but grunting when pressure is made over the abdomen. This is in striking contrast with the condition in the early afternoon. Liver dulness is present. There is slight dulness in the flanks. There has been no nausea nor vomiting. Leucocytes, Sept. 14, 1 P. M., 7400; 2 P. M., 2300; 3 P. M., 3500; 4.30 P. M., 4000; 7 P. M., 6500; 9 P. M., 4000; 11 P. M., 3000.

Surgical consultation (Dr. Mitchell.) Exploratory operation is advised on the strength of the abdominal symptoms.

Operation.—Sept. 15, 1900, 12.50 A. M.; Mitchell; cocaine and chloroform. Exploratory laparotomy; no evidences of typhoid fever; free fluid in peritoneal cavity; injected vessels in peritoneum; closure with silver.

The patient was given two hypodermics of morphia before operation.

An incision was made at the border of the right rectus muscle, which was pulled to one side. The patient was rather excited and restless and whiffs of chloroform were given from time to time throughout the operation. On opening the peritoneal cavity there was found a small amount of clear, free fluid. The intestines were not distended, but both visceral and parietal peritoneum were much redder than normal, and the vessels over the peritoneum were injected. There were no other evidences of peritonitis. No enlarged Peyer's patches were observed. The gall-bladder looked normal. The abdomen was closed with silver.

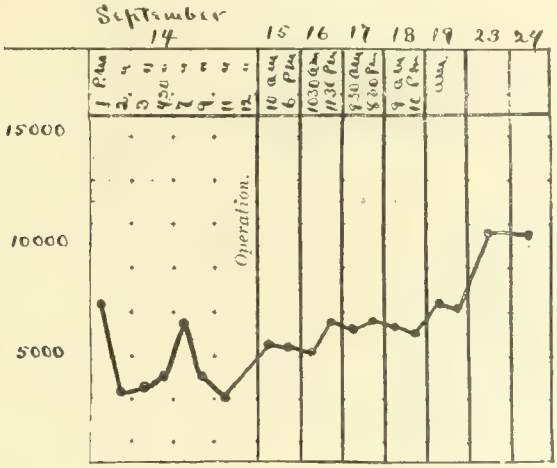
Sept. 17, 1900 (Dr. Mitchell).—After operation the patient's temperature dropped rapidly to 99, and for the past 48 hours has been normal. There was a corresponding drop in the pulse. There have been several fluid stools. His general appearance is suggestive of typhoid. He is dull and apathetic. The abdomen is very slightly distended, with some tenderness on the right side. The tenderness along the costal margin has almost entirely disappeared. Examination of the blood for malarial organisms is negative.

Sept. 27.—For the past ten days the patient has been running an irregular temperature, varying from normal to 103°. Repeated examination of the fresh blood for malarial organisms is negative. The leucocytes have ranged from 5,000 to 7,000. Abdominal symptoms have again been marked and are very similar to those before operation.

Oct. 1.—On the 27th of Sept. patient was put upon quinine, 5 grs. by mouth three times a day. His temperature immediately dropped. The leucocytes have ranged from 5000 to 7000. Abdominal symptoms have entirely disappeared.

Oct. 25.—The temperature has remained normal since the last note. There have been no abdominal symptoms. He is discharged well.

CASE XXI. LEUCOCYTE CHART.



(e) *Conditions Causing Abdominal Symptoms in which Operation was not thought to be indicated.*

In reviewing the eleven cases which comprise this group, it must be said that in some at least it seems difficult to understand why exploration was not done. The symptoms as viewed in the histories suggest very strongly some abdominal complication. In four of them the symptoms were apparently caused by abdominal distention with severe toxæmia; one is explained by iliac thrombosis, one by hæmorrhage, one most peculiarly by a termination by crisis, and two by a neurotic condition. In one other case the symptoms seemed to be especially gastric, and for another one no explanation can be given. In some of these the associated features give a clue to the cause. Those with marked neurotic symptoms are most apt to give difficulty in recognition only on the first manifestation. The cases with abdominal distention and pain along with local signs and perhaps leucocytosis are most puzzling. It is in these

especially that familiarity with the abdominal features which may occur without any complication is most important. The handling of many cases gives one a knowledge of the marked symptoms that may be associated with distention. The cases of hæmorrhage must always be difficult and we have found more possibility of error here than in any other condition.

CASE XXII.—*Typhoid fever; abdominal symptoms marked throughout illness; death; autopsy.*

Explanation.—Intestinal distention and profound toxæmia.

F. A. N. (Med. No. 11471), male, white, aged 19, was admitted to the medical service June 22, 1900, on the 8th day of typhoid fever. The Widal reaction was positive on July 7. During the week previous to admission he had had abdominal pain and diarrhœa, followed by constipation, and on one occasion vomiting.

On admission the temperature was 103°. The patient was in good condition. The abdomen was natural with slight tenderness and resistance. Leucocytes, 5200.

July 6.—The temperature averaged between 102° to 103° for the first few days, gradually falling during the past week and not rising above 101° for the past three days. His abdomen continued slightly tender, the muscles were held stiffly. There was no muscle spasm and no especial tenderness on palpation. About 5.30 this afternoon he began to complain of abdominal pain which was not very severe until 7 P. M., when it seemed to be quite sharp. His bowels have moved. There was no muscle spasm. There was slight abdominal rigidity and considerable tenderness over the whole lower abdomen. The leucocytes were 9500 at 7 P. M. and 14,000 at 8.30 P. M.

9 P. M.—The patient is still complaining of pain. His temperature has risen from 99° at noon to 103.6°; pulse, 112. The abdomen is somewhat distended and full, tender especially in its lower portion; no muscle spasm. Liver dulness extends to the costal margin. Leucocytes, 9.30 P. M., 8500.

10 P. M., Dr. Futcher.—The temperature has risen to 104.5°; pulse, 100, of fair volume. The abdomen is not distended. Respiratory movements are slightly limited below the umbilicus. There is tenderness on pressure, especially in the hypogastric region. There is no nausea. The abdominal muscles are no more rigid than they have been, though there is a trifle more resistance on the right side. The percussion note is everywhere tympanitic; no dulness in the flanks. Leucocytes at midnight, 10,000.

July 7, 1900.—Leucocytes at 8.30 A. M., 13,500. The patient is still complaining of abdominal pain.

11.30 A. M.—Leucocytes, 12,000; 6.30 P. M., 9000.

July 8, Dr. Futcher.—The temperature continues high. There is slight abdominal pain; no distention. Leucocytes, 12,000.

July 9, Dr. Futcher.—The abdominal pain is slightly increased. There is no nausea or vomiting. There is no distention; no localized tenderness. Hepatic flatness extends to the costal margin. There is no tenderness along the femoral vessels. Leucocytes, 7.30 P. M., 10,000.

July 10, 3 A. M.—About 1.20 A. M. the patient began to complain of of much more severe abdominal pain, which was most marked in the mid-abdomen. He vomited once at 2 A. M. At 2.30 A. M. the leucocytes were 10,800. Expression is rather anxious; no cyanosis; no perspiration; fingers are a trifle cold; pulse has changed but little. Since yesterday, at 5.30 P. M., the abdomen has been decidedly more distended. Respiratory movements are still well seen. The costal grooves are almost obliterated. General tenderness is marked, a trifle more on the right side. There is no muscle spasm. Tympany is more marked throughout and extends 8 cm. above the costal margin in the mammillary line; no dulness in the flanks.

5.30 A. M.—The patient has expelled considerable gas. The abdominal distention has almost disapeared. Hepatic flatness extends almost to the costal margin.

Leucocytes, 3.45 A. M., 11,000; 9 A. M., 11,000; 5 P. M., 7000; 8 P. M., 5000.

July 11.—The patient is comfortable. The abdomen is distended. Liver dulness is 7 cm. above the costal margin in the mammillary line. The temperature remains high. Leucocytes, at midnight, 5000.

2 P. M.—The patient is again complaining of severe abdominal pain. He has been nauseated and has vomited two ounces of bloody fluid. The abdomen is much more distended than usual; no muscle rigidity nor spasm; no marked tenderness. The distention is apparently due to gas in the intestine. The passage of a rectal tube is ordered. Leucocytes, 9 P. M., 4600.

July 12.—Leucocytes, 2 P. M., 2900; 9 P. M., 2700. The abdominal distention has been somewhat relieved by turpentine stupes and enemata and the passage of a rectal tube. There is muscular twitching. The patient's general condition is decidedly worse.

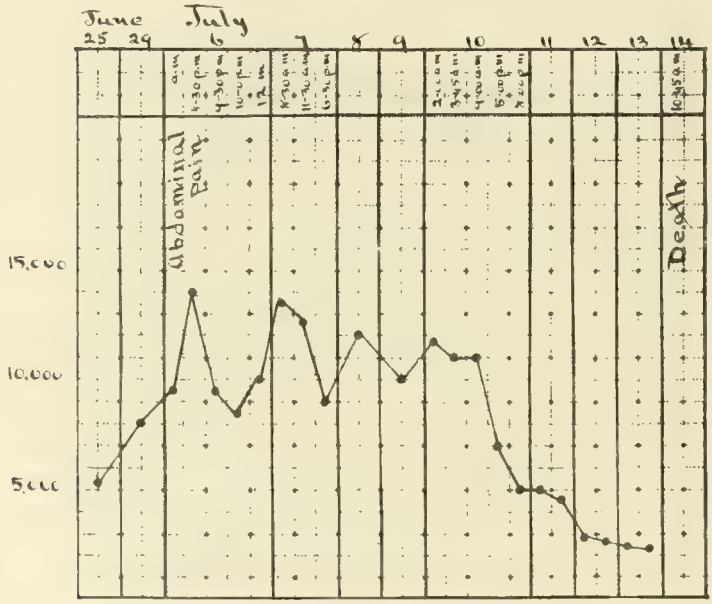
July 14.—The leucocytes yesterday were 2400 at 2 P. M., 2300 at 8.30 P. M. The temperature continued elevated. There was nausea with occasional vomiting. The abdominal distention continued. There was never any great tenderness nor muscle spasm. The patient's condition gradually became worse and he died at 1.45 this morning.

Autopsy.—Typhoid fever. Extensive ulceration of the ileum and distention of the intestines with gas. No perforation. No evidence of peritonitis. The man died of profound toxæmia.

Remarks.—The abdominal symptoms were marked throughout the whole course of the patient's illness, both before and after admission to the hospital. During the last two weeks of his illness he was watched very closely with the possibility of a perforation

ever in mind. The increase of the abdominal symptoms with distention, and the subsidence of these symptoms with the relief of the distention, pointed to it as a cause of his symptoms. The slight tenderness and rigidity with the entire absence of muscle spasm and the free respiratory movements were opposed to peritoneal involvement. An interesting feature is the gradual fall in leucocytes during the last two weeks, a drop from 14,000 to 2300, correponding to the gradual increase in his toxæmia and decrease in resistance.

CASE XXII. LEUCOCYTE CHART.



CASE XXIII.—*Typhoid fever; abdominal symptoms; recovery.*

Explanation.—Toxæmia and intestinal distention.

H. W. (Med. No. 12027), colored, female, aged 19; was admitted to the medical service on Oct. 16, 1900, on the 5th day of typhoid fever. On admission she was very ill; temperature, 106°; pulse, 140; leucocytes, 12,500. The abdomen was distended, the liver dulness being much diminished; no rigidity; no tenderness.

During the next few days the patient was very ill, her temperature frequently reaching 106°, and the pulse averaging from 150 to 160. The leucocytes during this time varied from 4000 to 17,500.

From Oct. 24 to Nov. 1, the general condition was better. The temperature and pulse had fallen. The leucocytes varied from 4000 to 6500.

Nov. 3.—The patient suddenly became much worse. Her temperature, which had averaged about 102°, rose to 104°, the pulse from 118 to 152. With this there was complaint of abdominal pain.

Nov. 3, 11 P. M., Dr. Futcher.—The general appearance is good. Pain in the abdomen became especially severe after the last tub. It is referred to the umbilical region. The abdomen is distended; respiratory movements free throughout; considerable general tenderness; no muscle spasm; no rigidity. The liver dulness is markedly diminished in the nipple line. Leucocytes, 15,800.

Nov. 4, 10 A. M., Dr. Futcher.—The general condition is much the same. Turpentine stupes have relieved the abdominal pain. The temperature is 103°; pulse, 140; leucocytes, 14,000.

11 P. M.—Leucocytes, 12,000.

Nov. 5.—The patient still complains of abdominal pain except when the stupes are applied. She lies with the knees drawn up. The temperature is 105.2°; pulse, 176; respirations, 40. The abdomen is everywhere slightly tender. There is no rigidity nor muscle spasm. Liver dulness is much less than at last note. The patient has vomited repeatedly after nourishment. Leucocytes, 12,000.

Nov. 5, 10 P. M., Dr. Osler.—The abdomen is markedly distended; respiratory movements are well marked, in fact quite free to the pubes. There is no special tension of the abdominal walls and no special tenderness, patient only wincing on deep pressure.

Nov. 6.—The temperature has risen to 106; pulse, 172; leucocytes, 12,000. Her general condition is much the same.

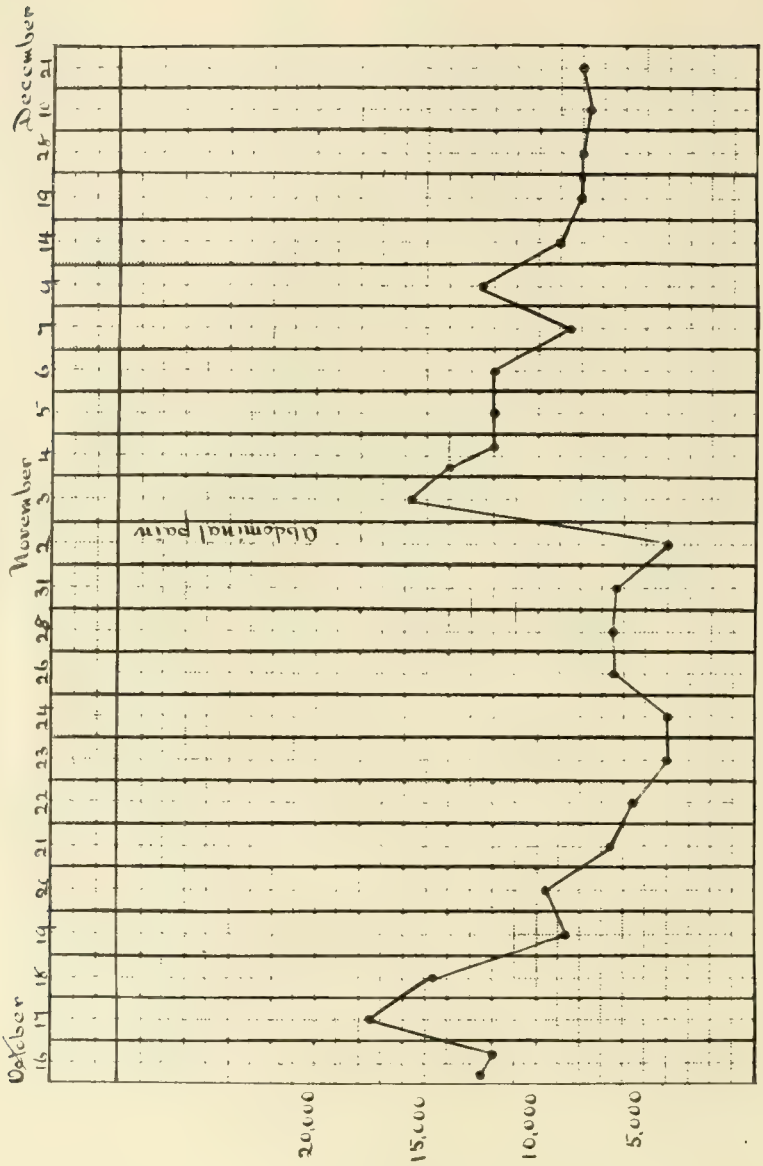
Following this the patient's general symptoms were very severe for some days, but the abdominal symptoms were much less marked, though slight general tenderness persisted for five days, during which time the leucocytes varied from 8500 to 12,500. The subsequent course was uneventful.

Remarks.—In this patient the sudden change in the general condition with much higher temperature and increased pulse rate and respiration, along with the abdominal features, suggested an acute complication. The marked toxæmia and distention and the fact that the abdominal symptoms did not increase in severity spoke against this. The frequent vomiting was, however, a very suggestive symptom. There was nothing to explain the leucocytosis on admission.

Case XXIV. *Typhoid fever; abdominal symptoms; no operation; recovery. Explanation.—Abdominal distention.*

E. H. (Med. No. 11833), female, black, aged 14; was admitted to the

CASE XXIII. LEUCOCYTE CHART.



medical service on Sept. 5, 1900, on the 8th day of typhoid fever. Her temperature was 103.8°, rising to 105° on the following day and continuing high during the next three or four days. The Widal reaction was obtained on the 18th day.

On admission the patient was in good condition, though dull and drowsy. The abdomen was rather distended and tense without tenderness. Liver dulness was obliterated below the 7th rib by the abdominal tympany.

Sept. 7, Dr. McCrae.—The abdomen this morning was negative. About 2 this afternoon she vomited and complained of pain in the abdomen. At 3.30 P. M. the pulse was rapid, 138; respirations 38. The abdomen was full, symmetrical, with well marked respiratory movements and some slight resistance and rigidity of the muscles on gentle palpation; no dulness in the flanks. During the remainder of the day the condition was much the same. She complained of abdominal pain. The walls were soft, but the right less so than the left.

Sept. 8, 5 A. M., Dr. McCrae.—The patient has vomited a small amount of fluid. The abdomen is rather full; the respiratory movements are well marked. Great pain is complained of on deep palpation, especially in the right iliac fossa, where there is marked gurgling. The abdomen is full; no muscle spasm: The general look of the patient is good though there is a suggestion of abdominal facies.

Sept. 8, 8.30 A. M.—There is a marked change since 5.30 A. M. The patient is quieter and allows the abdomen to be palpated without any complaint. The right side is slightly more tender than the left. The leucocytes have ranged from 3000 to 5000 during the past 24 hours. After turpentine stupes the distention of the abdomen gradually disappeared and the patient's symptoms soon subsided. There was no recurrence of the abdominal symptoms and she made an uninterrupted recovery.

Remarks.—The condition of the patient at one time certainly suggested the possibility of perforation; the abdominal pain with rather sudden onset, the nausea and vomiting, the abdominal distention with rigidity and tenderness all favoring this opinion. The rapidly increasing distention with no accompanying increase in tenderness or rigidity, the entire absence of muscle spasm, the good character of the pulse, and the general condition of the patient suggested that the symptoms were probably due to the distention alone, which fact was substantiated by the rapid disappearance of the symptoms after relief of the distention.

Case XXV.—*Typhoid fever; abdominal symptoms; no operation. Explanation.—Abdominal distention.*

S. M. (Med. No. 12132), female, colored, aged 12; was admitted to the

medical service Nov. 6, 1900, on the 10th day of typhoid fever. The Widal reaction was positive on the 11th day.

On admission she was very ill; temperature 103°; pulse 140. The abdomen was slightly distended; respiratory movements were present but diminished below the navel. There was some rigiuity, more marked on the right side, where pain was complained of on deep palpation. There was no muscle spasm. Leucocytes were 13,000.

For six days after admission the course was moderately severe; but the general condition improved.

Nov. 12.—The patient complains of abdominal pain, much increased while in the tub. This began at 5 A. M. The temperature at 4 A. M. had been 104.6°; pulse 160. At 6 A. M. the temperature was 101.2°; pulse 144.

8.30 A. M., Dr. Futcher.—The child was found lying on the left side with the knees drawn up; pulse 160; respirations 32. There has been no nausea or vomiting. The extremities are warm. The abdomen is not distended. There is complaint of general abdominal pain. The respiratory movements are somewhat limited below the navel, the abdominal walls a little rigid, the left side a little more so than the right. The greatest tenderness is in the left iliac fossa to the left of the navel, but there is no muscle spasm. Liver dulness just reaches the costal margin. Leucocytes, 9700.

Later in the day the pain seemed less, the rigidity of the abdominal wall was diminished. On deep palpation to the left of the navel there was still tenderness. Leucocytes, 7800.

Nov. 14.—The abdomen is still distended, the walls everywhere rather tense. There is no muscle spasm and no especial tenderness. During all this time the temperature has shown no especial change.

Nov. 15.—The patient was removed by the parents against advice. On discharge the abdomen was still distended with slight tenderness present.

Remarks.—Perhaps the most important point in this case is that in spite of the very severe general symptoms, the abdominal signs were comparatively slight and did not increase in severity. They were probably due to distention. The patient left the hospital against advice and was lost sight of.

Case XXVI.—*Typhoid fever; abdominal symptoms associated with pain in the legs following an enema; recovery. Explanation—Iliac thrombosis.*

C. B. (Medical No. 11719), white, male, aged 21; was admitted to the medical service on Aug. 13, 1900, on the 8th day of typhoid fever. The Widal reaction was positive on the 16th day. The patient was admitted in good condition with a temperature of 104° and pulse 96. The leucocytes were 9000.

Aug. 22.—The leucocytes are 11,000. He complains of some pain in the legs. On examination there is nothing special to be made out, no thrombosis, no tenderness over the veins.

Aug. 24.—Leucocytes, 12,700.

Aug. 27.—Leucocytes, 17,000. The patient was given an enema about 6 this morning, after which he complained of severe abdominal pain.

Aug. 28, 11 A. M., Dr. McCrae.—The patient's general condition is good; temperature 101°; pulse 88. The abdomen is full, everywhere somewhat tender; respiratory movements present, but no rigidity or muscle spasm. Liver dulness in the nipple line is slightly diminished. The patient also complains of pains in the legs. Nothing is to be made out on examination. There is no tenderness over the veins. Leucocytes, 20,500. During the day he complained at times of pain in the abdomen. His temperature averages about 101°. There is no increase in the abdominal symptoms.

Aug. 29.—The condition is much the same. He still has pain in the abdomen and in the legs.

Aug. 30.—The pain in the legs is less. Little complaint is made of the abdominal pain. The general condition is good. Leucocytes, 20,500. His subsequent history was uneventful. The abdominal pain disappeared. The tenderness in the legs remained for some time. There was slight swelling of both legs. No definite thrombosis, however, was to be made out.

Sept. 3.—Leucocytes, 14,800. Recovery has been uninterrupted, except that the patient complained for some time of the tenderness, especially in the left leg.

Remarks.—The abdominal facies in this case was quite marked and associated with the marked leucocytosis, suggested an acute abdominal complication. The pain in the legs for some days before, associated with some leucocytosis, also the fact that the tenderness in the abdomen was rather more marked over the course of the iliac veins, along with the tenderness in the legs, all suggested thrombosis.

In addition to this the fact that we had had a previous lesson concerning the abdominal features which might be associated with iliac thrombosis suggested this as an explanation of the symptom. It is of interest to note that the abdominal pain followed the giving of an enema.

CASE XXVII.—*Typhoid fever; abdominal symptoms with intestinal hæmorrhage; three relapses; recovery.*

Explanation.—Intestinal hæmorrhage.

L. D. (Med. No. 13246), white, female, aged 12; was admitted to the medical service on Aug. 5, 1901, on the 4th day of typhoid fever.

The Widal reaction was positive on the 7th day. She gave a history of abdominal pain some days before admission but came in in good condition; temperature 102.5°. The abdomen was flat, showing slight general tenderness on palpation.

Aug. 6, 1901.—Leucocytes, 12,600.

From August 6th, to the 14th the course was uneventful, the temperature being about 103°; pulse 104 to 120. Some abdominal pain was complained of. The abdominal examination was negative. The leucocytes varied from 4400 to 7200.

Aug. 15, 9 A. M.—The patient had a hæmorrhage of about 150 cc. of fresh blood. Several others followed, the total amount being about 500 cc.

11 A. M., Dr. Futcher.—There is a slight general pallor of the face. The patient has at times a somewhat drawn expression. The temperature is 101.4°; pulse 144; leucocytes 12,000. There has been some pain in the abdomen since the first hæmorrhage at 9 A. M. The abdomen is not distended; respiratory movements are free throughout. There is quite marked tenderness, but no rigidity nor muscle spasm. Liver dulness comes to the costal margin in the nipple line.

During the day she had two more hæmorrhages. The leucocytes at 5 P. M. were 6800.

The patient was restless. She was given morphia, gr. 1/10, hypodermically and one opium pill every two hours for three doses. For a time her condition was very serious. There was no pulse at the wrist and the pallor was marked. No complaint was made of abdominal pain, but whenever the abdomen was touched the patient screamed.

Aug. 16.—The general condition is somewhat better. Leucocytes, 4000. In the afternoon she made complaint of abdominal pain.

6 P. M., Dr. Futcher.—The patient complains of severe pain in the lower right quadrant of the abdomen. The expression of the face has not materialy changed, but at times there is a peculiar pinched expression about the mouth. The abdomen is not distended, respiratory movements being freely marked throughout. There is great tenderness in the lower right quadrant of the abdomen and some general tenderness and spasm.

The patient was seen by Dr. Mitchell. It was found that the sensitiveness was fully as marked over the right thigh as over the abdomen, and at 6.30 P. M. there is tenderness over the abdomen but the muscle spasm and rigidity have entirely disappeared. Apparently the whole condition was of nervous origin. It is to be noticed that the child had voided urine in the meantime which may have been a factor in the cessation of the symptoms. She had not voided previously since she was catheterized at 8 A. M.

Aug. 16, 11.45 P. M., Dr. Futcher.—The symptoms are practically identical with those seen at 6 P. M. The patient cries out with pain at times, which is not definitely located owing to her somewhat delirious condition. The abdomen is not distended. Respiratory move-

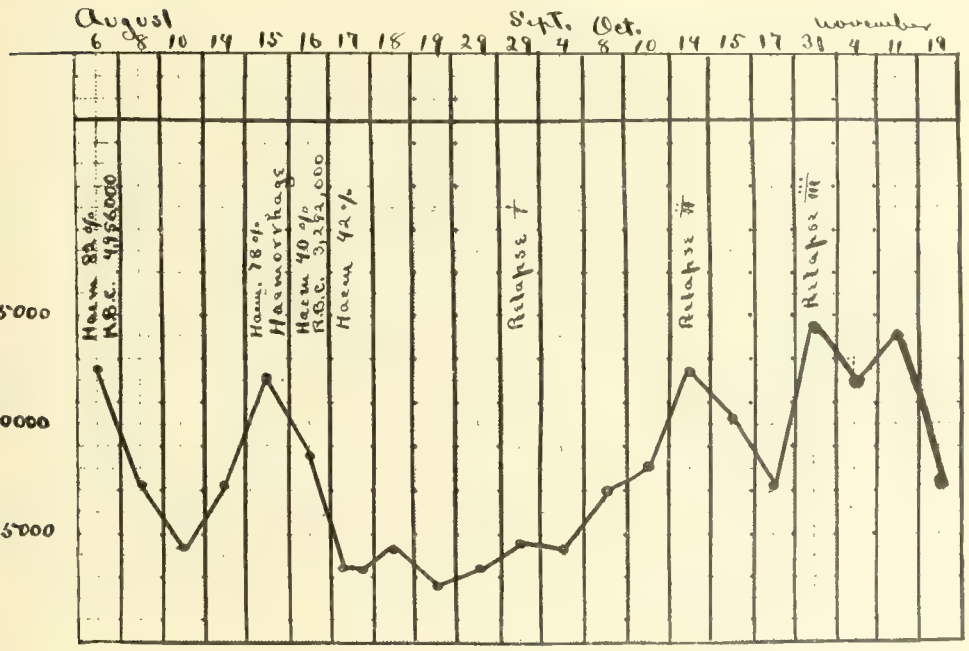
ments, if anything, are slightly less marked than at 6 o'clock. The slightest pressure over the right iliac and lumbar regions causes her to complain of pain. There is definite rigidity and muscle spasm on the right side but none on the left. Liver dulness still comes to the costal margin. There has been no vomiting.

Aug. 17.—The patient's condition is much better. The pulse has dropped in rate, the abdominal symptoms are less marked, although there is some tenderness on palpation. Leucocytes, 3300.

Aug. 18.—The abdomen is not distended; respiratory movements are fairly free; tenderness in the right iliac fossa is much less. Leucocytes, 4200.

Following this the patient had an extremely protracted illness with three relapses and three recrudescences. She was discharged well on the 135th day. There were no abdominal symptoms after those noted.

CASE XXVII. Leucocyte Chart.

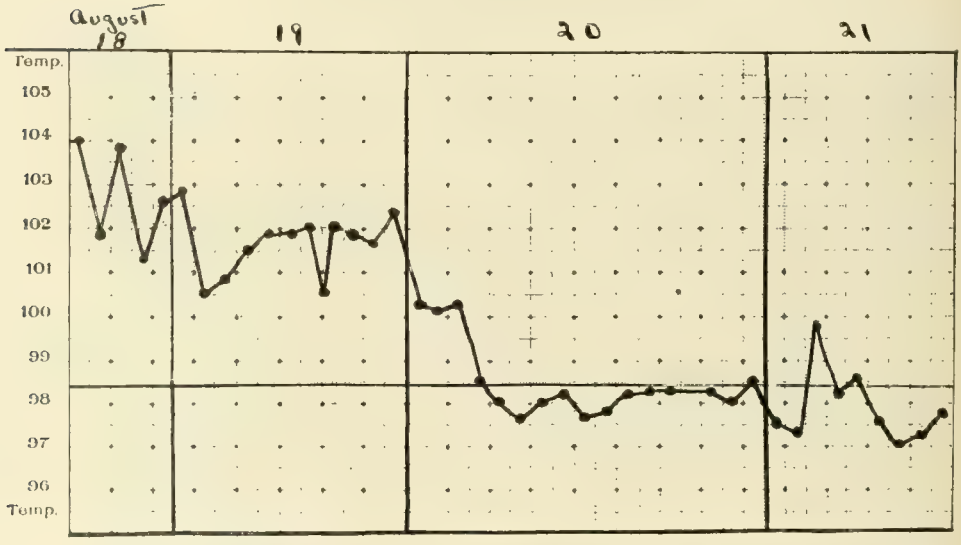


Remarks.—A point of special interest in this case is the onset of abdominal symptoms with hæmorrhage. The possibility of perforation occurring with hæmorrhage and being overlooked was prominently in our minds.

The sudden onset of severe symptoms on Aug. 16, suggested that perforation had occurred, but their total disappearance within half an hour to return a few hours later spoke against this complication.

For a full report and discussion of this case see Warfield, Johns Hopkins Hospital Bulletin, July, 1902.

CASE XXVIII. TEMPERATURE CHART.



CASE XXVIII. *Typhoid fever; termination by crisis on 14th day accompanied by abdominal symptoms; recovery.*

F. H. (Medical No. 11705), male, colored, aged 17; was admitted to the medical service on Aug. 9, 1900, on the 3d day of typhoid fever. The Widal reaction was given on the 15th day.

On admission the general condition was good; temperature 103°; pulse 104; the abdomen was not distended. The patient complained of some pain in the right iliac fossa. The abdominal walls were held so firmly that satisfactory palpation was impossible. Liver dulness came to the costal margin. For the next week the temperature was high, but the general condition was good. At times slight abdominal pains were complained of.

Aug. 20, 11 A. M., Dr. McCrae.—The patient was found complaining of sudden pain. At times the face has a distressed expression. The pulse is only 64. The abdomen is flat; respiratory movements are present; pain is complained of about the navel. On palpation there

is no rigidity and no muscle spasm and no tenderness on ordinary handling. On deep pressure there is slight tenderness over the lower abdomen. Liver dulness in the nipple line comes just about to the costal margin. Leucocytes, 15,000.

An hour later the patient was quiet. The abdominal walls were held a little more tensely, and the patient flinched rather more on pressure, especially on the right side. Leucocytes, 12,000.

The temperature was interesting. On Aug. 19, it averaged about 102.5°. At 2 and 6 P. M. on Aug. 20, it was 100°; at 8 A. M. it had fallen to normal; at the onset of abdominal pain on the 20th, it was 98°. During the remainder of Aug. 20, it contained subnormal.

After this the course was uneventful. The temperature continued normal and the patient made an uninterrupted recovery. The termination was by crisis and with it occurred the suspicious abdominal symptoms noted above.

Remarks.—The special point of interest in this case is the termination by crisis on the 14th day, the temperature falling nearly 5 degrees within about 8 hours. This was associated with marked abdominal symptoms as noted above and a leucocytosis of 15,000. The sudden onset of abdominal pain with some rigidity of the walls and drop in the temperature, along with the leucocytosis, all suggested some complication. The advisability of exploration was considered, but the absence of general features, the fact that the pulse rate did not increase, and the clearing up of the symptoms under constant observation decided us against this.

Case XXIX.—*Typhoid fever; abdominal symptoms; recovery.*
Explanation.—Gastric disturbance.

J. G. (Medical No. 12987), white, male, aged 18; was admitted to the medical service on June 7, 1901, on the 14th day of typhoid fever. The Widal reaction was positive on the day after admission. He stated that for two days before admission he had had abdominal pain, which had been more or less constant, and severe enough to prevent his sleeping at night. The pain had been general and severe enough to make him cry out. There had been some nausea but no vomiting.

On admission he was very ill; temperature 104°. The abdomen was distended; respiratory movements present but diminished below the navel. On palpation there was everywhere rigidity; some tenderness in the left iliac fossa; no definite muscle spasm. Liver dulness was slightly diminished. Leucocytes, 9000. At 10 P. M. on the day of admission he complained of severe abdominal pain which was not localized, but diffuse. About 11 P. M. he was nauseated and attempted to vomit. During the next hour he complained of severe abdominal pain, with which he at times cried out. The leucocytes at midnight were 9000.

June 8, 2 A. M., Dr. Mitchell.—There is slight general distention of the abdomen. The respiratory movements are present, though slight in the lower abdomen. There is an expiratory grunt. The abdomen is held tense. There is slight general tenderness, which is most marked to the right and just above the navel. There is no protective spasm. Deep pressure is possible. No difference in rigidity in the two recti can be determined, although the tenderness is distinctly more on the right side. Liver dulness is somewhat diminished in the nipple line. His general condition is fairly good. There is no sweating.

Leucocytes, 2.15 A. M., 9000; 3.30 A. M., 8500.

3 A. M.—The patient has severe nausea and makes frequent violent attempt to vomit, but has vomited only about one-half ounce of bile-stained fluid.

4 A. M., Dr. Mitchell.—The patient is quiet. The expiratory grunt has disappeared. The extremities are warm. There is practically no change in the abdomen; no increase in rigidity in the past two hours; no muscle spasm. From 5.30 A. M. to 8.30 A. M. he was frequently nauseated and vomited once. He did not complain of any increased abdominal pain. At 8.30 A. M. the leucocytes were 8500.

10 A. M., Dr. Osler.—The patient is not collapsed. There is no sweating; some lividity of the skin; the pulse is regular, 112; the abdomen is symmetrical. There is no special distention, though the abdomen is a little fuller above than below the navel. The respiratory movements are chiefly in the upper abdomen. There is no movement below the navel. On palpation there is no general pain on deep pressure. The abdominal walls are held stiffly, but there is no special point of increased tension. There is only about one finger's breadth of liver dulness in the nipple line.

In the two hours following this note the patient vomited twice and hiccoughed several times.

12.30 P. M.—Leucocytes, 13,000 after vomiting.

3.30 P. M.—Leucocytes, 7000.

5 P. M., Dr. Mitchell.—The abdominal condition is about the same as when seen by Dr. Osler in the morning. There is little movement below the navel, although the walls are tense. There is no rigidity on deep palpation, no suggestion of muscle spasm. The tenderness is rather less than it was this morning.

From 7 to 9 P. M. the patient was nauseated and several times vomited bile-stained fluid. He has made no complaint of abdominal pain. There was no tenderness on pressure. The abdomen was decidedly softer than this morning.

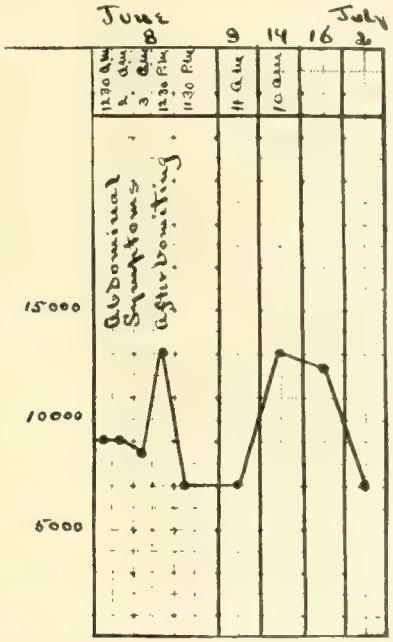
11.30 P. M.—Leucocytes, 7000.

June 9.—The patient is more comfortable; no nausea and no vomiting after 1 A. M. The abdomen is still slightly full and the recti rather tense, but on the whole the abdomen is much softer than it was before. There is no tenderness. Leucocytes, 11.30 A. M., 7000.

June 10.—The condition is much the same. During these two days the temperature has been much lower, having dropped from 104° on admission on June 7th to 99.5° on the 8th, after which it remained between 100° and 101°.

June 11.—The abdomen is still somewhat tender, but otherwise negative. Following this there were no symptoms of any importance. The patient made a good recovery.

CASE XXIX. LEUCOCYTE CHART.



Remarks.—After reviewing this case it is difficult to see why an exploration was not done. The marked general symptoms, the nausea, vomiting and hiccoughing, the abdominal pain and slight tenderness, along with the drop in temperature were all suggestive. The fact, however, that the local symptoms did not increase in severity, the general condition was so good and the pulse rate was undisturbed, spoke against it.

CASE XXX.—*Typhoid fever; repeated abdominal symptoms; recovery. Explanation.—General neurotic condition.*

A. R. (Med. No. 11683), male, white, aged 22, was admitted to the medical side August 5, 1900, on the 4th day of typhoid fever. The

Widal reaction was positive on the 10th day. Since onset he had had almost constant nausea and vomiting.

On admission his general condition was good. The temperature was 104.6° and remained high for several days after admission. The abdomen was natural; respiratory movements were present. There was no abdominal rigidity, tenderness nor muscle spasm. Leucocytes, 8000.

Aug. 7.—Leucocytes, 6000.

Aug. 9, 10 P. M.—The patient has just complained of severe abdominal pain. At the same time there was nausea and vomiting. The pain was not localized. There is general abdominal tenderness, no distention; respiratory movements present; no muscle spasm. Leucocytes, 6000.

11 P. M.—Leucocytes, 7000.

12 midnight.—The patient is evidently suffering intense pain, and cries out so that he can be heard throughout the ward. He was found lying on his left side with the thighs flexed and complains of severe pain in the umbilical region. His faced is flushed; the extremeties are warm; temperature, 104°; pulse of good volume, regular, 112. The pupils are widely dilated. The abdomen is not distended, symmetrical; respiratory movements free throughout. On palpation pain is everywhere complained of. The muscles are rigid but no definite muscle spasm is made out. The liver dulness reaches the costal margin. There is no dulness in the flanks. There is marked hyperæsthesia practically everywhere throughout the body, especially on pressure over the muscles. The patient has not vomited since the onset of pain.

Aug. 10, 12.15 A. M.—Leucocytes, 5000; 1 A. M., 6000.

1 A. M., Dr. Futcher.—The patient is still complaining of pain throughout the whole abdomen. He looks very nervous and apprehensive. The pulse is good, 112. There has been no drop in temperature. The abdominal muscles are still rigid, more so on the right side than on the left. Rectal examination is negative, except that the patient complains of severe pain on pressure posterior to the bladder.

8 A. M.—Leucocytes, 5000.

During the day the patient was comparatively comfortable. The leucocytes between 1 P. M. and 10 P. M. in five counts varied from 9000 to 11,000.

10 P. M.—The patient complains again of severe abdominal pain, crying out loudly. He complains also of nausea but has not vomited. The pain is general throughout the abdomen. There is no distention but the rigidity is as before.

The pain lasted but a short time and afterward the patient was comfortable.

Aug. 11, 8 A. M.—Leucocytes, 7000.

6 P. M.—The patient had another attack of severe abdominal pain.

8 P. M.—Leucocytes, 8000.

Aug. 12.—The patient's condition is good; pulse 100. There is no abdominal pain.

During the following week the temperature continued high. The general condition was good. He was extremely nervous and neurotic and much alarmed about himself. The leucocytes during this time varied from 7000 to 10,000.

Aug. 19.—He had another attack of abdominal pain exactly like the preceding ones, and again one on Aug. 21, the leucocytes on both occasions being about 5000. After this his progres was uninterrupted and he made a good recovery.

Remarks.—The attacks of abdominal pain were accompanied by several striking features. The patient cried out loudly, complained bitterly on palpation of the abdomen and throughout showed so many neurotic features that our suspicions were aroused even with the first attack of pain. The nausea and vomititng whieh had been present from the onset were disturbing features. The abdominal tenderness and at times rigidity more marked on one side suggested an abdominal complication, but were offset by the fact that at times he showed great hyperæsthesia over the muscles generally. The absence of distention and muscle spasm and of any great change in the abdominal condition were against abdominal complication. After the first attack of pain the others caused but slight anxiety, the neurotic feature in the case being well recognized after our first experience. Neither the pulse, respirations, nor temperature showed any great change.

Case XXXI.—*Typhoid fever; abdominal symptoms; recovery. Explanation—General neurotic condition.*

N. K. (Med. No. 11744), female, white, aged 22, was admitted to the medical service on Aug. 26, 1900, on the 13th day of typhoid fever. The Widal reaction was positive on the day after admission. On admission the general condition was good; temperature, 105.5°; pulse, 120. The abdomen was symmetrical and not distended; respiratory movements were present; slight general abdominal tenderness; no rigidity and no muscle spasm. Leucocytes, 7500. There were no special features until Sept. 2. The leucocytes during this time ranged from 5500 to 8000.

Sept. 2.—The patient complained of severe pain in the right lower abdomen.

11.30 P. M., Dr. McCrae.—The patient was found lying on the left side with the knees drawn up, complaining of abdominal pain. There are no peritonitic suggestions in the facies; respirations, 28; pulse, 112. The abdomen is flat and symmetrical; respiratory movements are present, but pain is complained of on deep breathing and on pressure. On palpation the muscles are held tense and there is marked muscle spasm on the right side. The patient is evidently very nervous and by

distracting her attention the left rectus becomes normal but not the right, which continues rigid and great tenderness is complained of on palpation. The contrast between the two sides of the abdomen is very marked. (It was kept in mind that the patient's occupation was that of a nurse. She thought herself that she had appendicitis. It was considered possible that she might be feigning the symptoms of that disease. Her whole condition was rather suggestive of a neurotic state.)

She was seen again at 2.15 A. M. on Sept. 3. She had been sleeping since midnight and stated that she had practically no pain. On examination there was still some tenderness on the right side of the abdomen, but the rigidity and muscle spasm were much less. On Sept. 2, at 1 A. M., the leucocytes were 2500.

Sept. 3, Dr. McCrae.—The patient's condition is good. The abdomen is flat and shows free respiratory movements. On palpation there is definite tenderness in the right iliac fossa, and muscle spasm on any attempt at deep palpation. Nothing abnormal can be felt. Leucocytes, 4700. With these symptoms there is no special change in the temperature, which has not been above 101°, nor in the pulse rate. The subsequent history was practically negative.

Remarks.—The picture presented by this patient, who was a nurse, at the time of onset of abdominal symptoms suggested very decidedly that of some acute complication. How much her knowledge of disease had to do with simulating the symptoms it is difficult to say. There could be no question of the rigidity and muscle spasm on the right side of the abdomen. The general suggestion of a neurotic condition was of considerable help in arriving at the conclusion that no acute abdominal condition existed.

Case XXXII.—*Typhoid fever; abdominal symptoms; recovery; no explanation.*

W. S. (Med. No. 13255), white, male, aged 22, was admitted to the medical service on Aug. 7, 1901. While on the surgical side, with a pyogenic infection of the ankle, typhoid fever began and he was transferred to the medical side on the 7th day. At the onset he complained of some abdominal pain. Typhoid bacilli were obtained from his blood on the 6th day. On admission his condition was good; temperature, 103°. The abdomen was moderately full; the walls were soft; there was slight general tenderness, most marked in the right iliac fossa. Liver dulness came to the costal margin. The course was uneventful until Aug. 14, when the patient, while in the tub, complained of sudden pain in the lower right quadrant of the abdomen. This gradually increased so that he cried out and could be heard some distance from the ward.

Aug. 14, 9 P. M., Dr. Futcher. The patient was found lying in dorsal decubitus, still complaining of pain in the lower half of the abdomen, somewhat less severe than a short time previously. The facial expression is unchanged; pulse, 72; respirations, 20. The abdomen is natural; there is no distention. The respiratory movements are free throughout. On deep palpation there is definite tenderness in both iliac fossæ, aparently equal on both sides; no rigidity nor muscle spasm. Liver dulness in the nipple line is 5 cm. above the costal margin. There is no nausea. Leucocytes, 7100 at 9 P. M.; 6500 at 10 P. M.; 4300 at 11 P. M. The temperature shows little change.

11.30 P. M., Dr. Futcher.—The patient has been fairly quite since 9 P. M. and has slept a few minutes. He has had occasional attacks of slight abdominal pain. There is no distention, no rigidity nor muscle spasm. Palpation causes much more pain in the lower abdomen than at 9 P. M. There is no change in the liver dulness. The pulse is 84: leucocytes, 2600.

Aug. 15, 2.30 A. M., Dr Futcher.—There is no material change. The patient is still complaining of slight pain. There is some general tenderness over the entire lower abdomen. The pulse 84; leucocytes, at 2 A. M., 3000; at 3 A. M., 2800.

8 A. M., Dr. Futcher.—There is still slight abdominal tenderness. The main feature is the rather striking retraction of the whole abdomen. The respiratory movements are somewhat diminished below the navel as compared with the last examination. There is no definite rigidity and no muscle spasm. Leucocytes, 4000 at 8.30 A. M.; 4000 at 10.30 A. M.; 5400 at 1 P. M.; 4000 at 3 P. M.

Aug. 16.—The temperature fell gradualy, reaching 99° at 8 A. M. The abdomen was still slightly retracted and there was some tenderness throughout. Leucocytes, 4000.

After this the course was uneventful and the patient made a good recovery.

Remarks.—In reviewing this case there do not seem to have been enough symptoms to have justified an exploration. The very sudden onset of pain with the marked local abdominal symptoms was very suggestive. Probably it was the absence of any marked change in the general condition, and especially the fact that the pulse rate was not affected, which influenced us in delaying until the symptoms had cleared up.

In reviewing the symptoms shown by the eleven cases in this group we find that in two there had been abdominal symptoms for some days before the onset of severe manifestations. The onset was sudden in eight and moderately sudden in the other three. In all abdominal pain was a prominent symptom at the onset, in

two accompanied by vomiting. Of the symptoms after the onset, there was a suggestive facies in two patients (one of whom had hæmorrhage), vomiting in four, in three accompanied by nausea. The temperature showed no special change in seven, rose after the onset of symptoms in two and fell in two (one being a termination by crisis). The pulse rose in rate in four and was unchanged in the others. The leucocytes were below 5000 in two, between 7000 and 10,000 in four, and above 12,000 in five cases. The highest leucocytosis was 20,500. What may be termed a "pre-perforative leucocytosis" was present in some. Of local abdominal symptoms pain was present in all, tenderness in all but one, rigidity in seven, and muscle spasm in two. The respiratory movements were diminished below the navel in four; distention was present in four and in the same number the signs were more marked on the right side than on the left side. Liver dulness was diminished in five, with distention in all. In four the patient persistently kept the knees drawn up.

Conclusion.—In the discussion of the abdominal features in this series of cases of typhoid fever we do not pretend to have drawn a picture applicable to all cases of perforation of the intestine. We have given the features of eight cases, but we realize that the next eight may show a quite different group of symptoms. We have tried to give the cases in which we were in error in full detail and they are perhaps more instructive than the others. The group of suspicious cases is worthy of study. The majority of descriptions of the disease give one little idea of their occurrence and features. In these cases there may be something in the general picture which influences one in advising operation or in holding back. The absence of progress in local symptoms was important in some of the doubtful group. It may be impossible to convey in words why one waits in a given case.

We do not wish to be understood as advising operation recklessly or in every suspicious case. The number of doubtful cases quoted above as left alone should prove the contrary. The early recognition of perforation is our only hope to diminish its mortality. To that end every means should be used and in certain cases exploration seems to us to be a perfectly justifiable procedure.

To summarize our two year's experience:

(1) Two hundred and seventy-five cases have been treated.

(2) Of these a certain number had unimportant complications, as boils or abscesses, the cultures from which in every instance yielded pyogenic cocci.

(3) Periostitis and perichondritis have been seen occasionally, always subsiding without surgical interference.

(4) Glandular affections, especially mastitis, occurred but were not serious.

(5) Abscess of the liver occurred once with recovery, the cultures being practically negative.

(6) There have been symptoms of cholecystitis in five cases of which three subsided without operation; one was operated upon and recovered, while in one the gall bladder ruptured and general peritonitis resulting in death followed.

(7) Appendicitis was suspected on admission in three cases and developed once during the course of typhoid fever.

(8) Perforation of the intestine occurred eight times. Of these seven were operated upon with two recoveries, a third dying of toxæmia after a week. All of these seven were recognized within nine hours except two in which hæmorrhage from the bowel accompanied the perforation. In one case operation was not advised because the patient was evidently in extremis.

(9) Exploratory laparotomy was done in two cases in which no perforation was found. In one the symptoms proved to be due to intestinal hæmorrhage; in the other to a low grade of peritonitis. The first died; the second recovered.

(10) Eleven cases with suspicious abdominal symptoms were not operated upon. Of these, two died and the autopsies showed no perforation. The remaining nine recovered.

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No attempt has been made to review the literature.

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THE SYMPTOMS, DIAGNOSIS AND SURGICAL TREATMENT OF URETERAL CALCULUS.

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The more general application of Radiography for the detection of calculi in the urinary organs has directed attention to the hitherto unrecognized frequency with which stones are impacted in the ureter, and the number of cases in which a diagnosis of ureteral calculus has been made, during life, has greatly increased.

While many cases of calculi found *post mortem* have been reported, those in which the stones have been recognized and removed by operation, are still comparatively few. Several articles have lately appeared, giving statistics of these cases, but in none have the tables been at all complete.

In some 9500 admissions to the gynecological department of the Johns Hopkins Hospital, four patients have been operated upon for ureteral calculi. These four cases and the ninety-seven, found during a seemingly thorough search of the literature, form the basis of this report.

The considerations of the subject will be taken up in the following order:

I, History; II, Etiology; III, Pathological Anatomy; IV, Symptomatology; V, Diagnosis, with differential diagnosis; VI, Treatment; VII, Prognosis.

I. History.

A calculus descending from the kidney may become lodged in any portion of the ureter, or, more rarely, a stone may be formed *de novo* in the ureter, and become adherent to its walls. Although ureteral calculi were recognized by the earlier medical writers, notably Morgagne,[1] Chopart was the first to give a clear description of such cases. In his *Traité des maladies des voies urinaires*, published in Paris in 1791, Chopart described very accurately the clinical aspects of the migration of calculi along the ureter, and gave such an excellent description of the symptoms caused by the arrest of a stone during its descent from the kidney, that little has since been added to the symptomatology of this affection.

Sir Astley Cooper in his Lectures on Surgery (London, 1820), gives his observations on several fatal cases, and advocates bleeding, opium and massage as the only practical measures for relief. Rayer, in his *Traité des maladies des reins* (1837), figures several ureters blocked with multiple stones, and was the first to call attention to these cases of "chain calculi."

Although little has been added to the clinical description of this affection since the work of Chopart and Cooper, great advances have been made in diagnosis. With the aid of the more exact methods of urinary examination, and more accurate means of abdominal palpation, much progress in diagnosis was made. Adding to these the recent methods of cystoscopy and ureteral catheterization, together with the help now afforded us by the Roentgen rays, we have means for diagnosis little hoped for by the earlier writers. With the more general use of these invaluable procedures, still greater progress will be made in the study of these important and often obscure cases.

Among the first to advocate operative measures for the extraction of a stone lodged in the ureter, was Morris,[2] of London, who in 1884 described the case of a woman of 55 years, who had suffered from renal colic for over two years. When seen by Morris

she had had complete anuria for six days and was in a condition bordering on collapse. On digital examination of the bladder, a calculus was found, impacted in the left ureteral orifice, and the author points out that a vesical ureterotomy might have been done, had the proper instruments been at hand. He then gives, for the first time, the indications for digital exploration of the vesical portion of the ureter, with a view to vesical ureterotomy, and pictures a lancet-shaped knife on a long shank, as a suitable instrument for the operation.

Previous to the publication of this paper of Morris, there are but three brief records in the literature of stones removed from the ureter by operation. In 1882, Bardenhauer (Case 34), reported the successful extraction of a calculus, by retroperitoneal ureterotomy, followed by suture of the ureter with fine silk. The other two cases are those briefly cited by Emmet (Cases 71 and 85), in both of which calculi were located in the lower end of the ureter, one being removed by an incision through the vaginal vault and the other by cystotomy. The earlier cases of operations on the ureter for calculus, which have been quoted throughout the literature and form the basis of the subsequent work, are those of extraperitoneal ureterotomy, reported by Kirkham and Ralfe and Godlee in 1889 (Cases 37 and 36); those of intraperitoneal ureterotomy published by Cullingworth in 1885 and Arbuthnot Lane in 1890 (Cases 61 and 62); that of combined intra- and extraperitoneal ureterotomy, by Hall in 1890 (Case 32); and that of vaginal ureterotomy by Cabot, also in 1890 (Case 73).

We owe much of our progress in the development of the operative technique to Israel[8] of Berlin, Tuffier[4] of Paris, and Morris of London.

There are now in the literature the records of 101 cases operated upon. It is upon these 101 cases that we have based our statistics and many of them will be quoted in the following pages.

A brief synopsis of these cases is appended.

II. Etiology.

Calculi found in the ureter may be divided, according to the location of their formation, into (1) primary and (2) secondary calculi. Belonging to the first group, are those which result from a deposition of urinary salts at some point along the ureteral wall, and in-

crease in size by subsequent precipitation; while secondary stones are formed in the pelvis of the kidney, and become lodged in the ureter during their descent into the bladder.

Calculi formed primarily in the ureter are very rare. While they may result from urinary deposits about the site of an old infection or ulceration, they more frequently occur after operations on the ureteral wall, as when a nonabsorbable suture becomes the nucleus of an irregular deposit of phosphates or urates. This precipitation may continue until the lumen of the ureter is almost occluded, as in a case which occurred at the Johns Hopkins Hospital, where a stone formed about a silk stitch which had been used to suture the opened ureter into the vagina (colpo-ureterostomy) for the purpose of relieving a stricture of the ureter. The patient suffered intense pain from vesical spasm, until the stone was discovered and removed. It was about 6 millimeters in diameter.[5]

Much the larger number of ureteral stones, however, are secondary to renal calculi, one or more of them becoming lodged somewhere in the ureter during their passage from the kidney to the bladder. As has often been pointed out, it is fallacious to regard the ureter as a passive conduit. It is practically a muscle, having a lumen through its center and possessing contractile power, as has the heart or the intestine. The urine is passed along this muscular tube by vermicular contraction, somewhat comparable to intestinal peristalsis. These periodical contractions are readily observed when the ureter is laid bare during abdominal operations, and undoubtedly assist in forcing urine along the tube. The presence of a foreign body, such as a calculus, beginning its descent, must cause a spasm of the muscular coats, and this we consider an important factor in causing the arrest of the stone. Added to this we have, in cases where infection is present, inflammatory reaction and swelling of the mucosa, which later cause thickening and rigidity of the ureteral walls and finally stenosis at the point of arrest. Such, as far as is known, are the general etiological factors.

There are certain predisposing causes, which are those commonly supposed to play a rôle in the production of nephrolithiasis. Among them may be mentioned,—

Sex. Renal calculi are said to be more common in males than in females, but the statistics of the 101 operative cases would seem

to indicate that calculi become impacted in the ureter more frequently in women than in men.

The sex is stated in 99 of the 101 cases, 44 occurring in men and 55 in women. It is probable that the anatomical relations of the pelvic portion of the ureter in the female predispose to the impaction of calculi in this situation. In 73 of the cases, the stone was located at or below the pelvic brim. Of these the sex is stated in 72, of which 44 were females, or 61 per cent.

Age. Renal calculi are more frequent during the earlier and later periods of life. So far as known, age is not a factor in considering the frequency of impaction. The youngest case operated upon was seven years of age and the oldest sixty-five, while the operation has been done most frequently—thirty-two times—on patients in the fourth decade.

Other etiological factors said to play a rôle in nephrolithiasis, such as heredity, sedentary occupations, the use of water from lime stone districts, and a diet largely of meat, need not be considered here.

Location of the impaction. A study of the operative cases reported, and the findings at *post mortem* examinations give three well marked points of predilection for the lodgment of ureteral stones, corresponding more or less accurately to the three points where there is diminution in the calibre of the tube. The first of these is from three to six cm. from the kidney; the second, (present in about three-fifths of the cadavers examined by Tanquary [6]) at the point where the ureter crosses the iliac artery; and the third, in the lower portion, where it passes through the bladder wall. Morris[2] gives statistics based on the twelve cases recorded in the *Transactions of the London Pathological Society*, as follows: In three, the calculus was found at the upper end; in five, one or more calculi were found at the lower end of one ureter and one or more stones were found in the opposite kidney; in two cases, both ureters were obstructed by calculi in the vesical orifice; in one, a stone was impacted in the left ureter, one inch from the bladder; and in the other, the lower opening of the right ureter was entirely obliterated by three calculi lodged in separate compartments, formed one above the other by constricting bands on the inner wall of the ureter. The largest stone was three inches long and three-fourths of an inch in diameter.

In tabulating the 101 operative cases I find that the position of the stone is stated in 98. In 20 (20.4 per cent) the calculus was located within 6 cm. of the kidney; in 14 (14.3 per cent), at or near the pelvic brim; and in 55 (56.1 per cent), the situation was within 6 cm. of the vesical orifice, leaving but about 10 per cent for all other locations.

Duration of the impaction. The length of time during which a calculus has remained in the ureter in any given case is difficult to determine, inasmuch as the symptoms may have been caused by the stone while still in the kidney, long before it began its descent. In the case of Mrs. J. (No. 84 in the table), later referred to, in which Dr. Kelly removed a stone from the right ureter, six cm. from the bladder, there had been no acute symptoms for eighteen months, when there was a definite attack of colic on this side, no calculus being subsequently passed as far as known. Four cases are reported of stones removed from the ureter, in which a nephrotomy at intervals of three, five, and seven months and one year previously, had revealed no stone in the kidney. The symptoms continuing, the second operation was undertaken and the calculus found. It must have been present in the ureter for at least these lengths of time. As an impacted ureteral stone is not incompatible with life, there is every reason to believe that they may remain many years. Desguin (Case 64) has described the case of a man, 34 years of age, who had suffered from paroxysms of abdominal pain since his fourth year, without any urinary symptoms. There was a localized point of tenderness on the right side, somewhat above McBurney's point. The diagnosis lay between ureteral calculus and appendicitis, the laparotomy revealing an irregularly shaped stone, weighing 10 grams, located in the right ureter at the brim of the pelvis. In this case, the supposition was, that the stone has been in this one position for thirty years.

III. Pathological Anatomy.

Characteristics of Ureteral Calculi. Ureteral calculi differ somewhat in appearance and composition, according as they are primary or secondary. Those primarily formed in the ureter, about an ulcerated area, above an inflammatory stenosis, or about foreign bodies, such as silk sutures, are for the most part light and porous. They are generally irregular, roughened, and covered by spicules,

and are usually densely adherent to the ureteral walls. Being most frequently composed of phosphates, they are soft in consistency and grayish white in color. Such a stone is minutely described by Tuffier,[4] who removed it from the mouth of the ureter, where it had probably been lodged for many years. It was the size and shape of a large English walnut and consisted of phosphates, showing a radial formation not unlike that seen in coral deposits.

Secondary calculi, on the contrary, are generally more regular in formation and are round or oval in contour. Like renal stones, they vary in composition. Those most commonly found are made up of uric acid, but we also have those formed of oxalates, phosphates and carbonates, or an admixture of these salts. Lange (Case 12) has described one, completely occluding the lumen of the ureter, made up of a fibrinous clot containing many small stones. Legueu (Case 20) has also reported a conglomerate stone, composed of numerous small uric acid calculi, while Tuffier (Case 27) extracted one as large as a small nut, having a center of uric acid the size of a grain of wheat, surrounded by a hard black friable substance, regarded by him as clotted blood. No stone composed entirely of cystin has yet been described.

In form, these calculi are usually elliptical, having their long axis parallel to that of the ureter. They resemble in size and shape an almond pit, date stone, or olive pit. Dr. R. B. Hall (Case 32), has described a horse-shoe shaped calculus, which acted as a ball valve, intermittently plugging the ureter and then allowing the dammed-up urine to escape suddenly, thus causing a tumor to appear and disappear in the region of the kidney. A stone (Case 80), removed from the lower end of the right ureter by vaginal ureterotomy, by Mundé,[1] of New York, had on its under surface a well marked groove which allowed the urine to flow by, there being no symptoms of renal retention. Stones which occur partly in the renal pelvis and partly in the ureter are sometimes *T* or *Y* shaped.

The size of ureteral calculi varies greatly, although they are seldom larger than 1 x 2 cm. Roberts reports a case in his *Urinary and Renal Diseases*, in which death occurred from the impaction of three stones, weighing together but 1⅓ grains. The largest ureteral stone yet reported is one, 17 cm. in length and 9 cm. in circumference, removed together with the left ureter by Israel

(Case 8). One found *post mortem* and preserved in St. George's Hospital Museum measures 5½ inches in length.

Stones lodged in the ureter may be single or multiple. Of the 101 cases on which our statistics are based, there were 12 in which more than one stone was found on the same side. Rayer[7] was the first to describe chain calculi, giving the name to a row of stones extending up the ureter. Such a case is mentioned by Agnew,[8] in Vol. II of his Surgery. In 1895 Postnikow (Case 5) removed a kidney and ureter, the latter of which contained fourteen stones, the largest being 11 x 19 mm. in size and adherent to the ureteral wall. Doyen (Case 76), in the same year, by a vaginal ureterotomy, extracted twenty-four stones, tetrahedronal in shape, with rounded angles and composed of uric acid. Whitehead (Case 95) also had a case of chain calculi, removing eleven of them *per urethram*. In Dr. Kelly's second case (Case 65), two calculi were removed which had been impacted in the right ureter 3 cm. from the kidney.

The pathological effects upon the kidney and ureter must now be considered. When the stone which has been lodged is small, or of such shape that the urine may flow past it without becoming dammed back, provided there be no infection of ureter or kidney, we may find normal structures. Atrophy of the kidney may occur after complete obstruction, and this may take place without symptoms. More frequently, however, the obstruction is sufficient to cause a dilatation of the urinary apparatus above the stone, causing, with sterile urine, a simple hydro-ureter and hydronephrosis. All grades of this condition are to be found, varying from a slight dilatation of the ureter, perhaps to one centimeter in diameter, with an associated increase in the size of the renal pelvis, to the conversion of the upper ureter and kidney into a huge hydronephrotic sac in which little of the secretory tissue of the kidney remains. This was the condition in the case of Miss K. (Case No. 65), from whose right ureter Dr. Kelly removed two calculi, by transperitoneal ureterotomy.

Miss K. (Gynecological No. 6598) had suffered for eight years with an intermittent swelling in the right side beneath the costal margin, the attacks coming on every three or four months. The appearance of this tumor was always accompanied by sharp colicky pain in the right side, fever, and gastro-intestinal disturbance, but there were never any urinary symptoms noted.

At operation the large dilated pelvis of the right kidney was exposed, pointing out anteriorly, the kidney cortex, which was only 0.5 cm. thick, being confined to the outer and upper pole. A free incision was made into the lower pole of the sac, evacuating 370 cc. of pale urine and with it a little, flat, dark colored stone, 6 mm. long. 3 cm. below the renal orifice, in the ureter, two stones were plainly seen and felt. These were 12 to 14 mm. in diameter, the lower one being somewhat the larger. The ureter below them was normal in size and appearance. An attempt to push the stones up into the dilated pelvis having failed, a longitudinal incision, 3.5 cm. long, was made in the ureteral wall, the stones were removed and the ureter sutured with twelve fine silk stitches. The abdomen was closed, with lateral drainage, and the patient made an uninterrupted recovery. During the three years which have elapsed since the operation, the patient has had no return of the trouble.

This natural tendency to a dilatation greatly facilitates the procedure advocated by Israel [3] and Tuffier,[4] that of pushing the stone up into the pelvis and removing it through a renal incision, either in the pelvis or in the cortex.

When the obstruction to the flow of urine is gradual and progressive, an atrophy of the kidney substance may take place, as in the cases where a small, shrunken, sclerotic organ is found.

Much more frequently, however, the urine becomes infected through an accompanying cystitis, in which case we have a septic dilatation, causing pyoureter, pyonephrosis, or pyelitis. For all of these forms of dilatation of the renal pelvis, Morris has suggested the name of *nephrectasis*. This term includes, therefore, hydro-, pyo-, and hemato-nephrosis.

The pathological findings in an infected case are well illustrated by the kidney and ureter of Case 11 (Gynecological No. 6872).

For three years Mrs. R. had suffered from intermittent attacks of dull aching pain in the left side and back, extending down into the left inguinal region. The attacks had come as often as once a week, and had been associated with oliguria. After the pain had passed away, the amount of urine was large, there having been voided in a short time as much as a quart, dark in color, with a sediment of pus. A catheter could be passed but a few centi-

meters up the left ureter. Distinct scratch marks were found on a wax-tipped bougie, and by this means the diagnosis of calculous stenosis of the left ureter was made. Before operating, it was ascertained by means of catheterization that the right kidney was secreting a large amount of practically normal urine.

The operation revealed a large left kidney, whose ureter was nodular and enormously enlarged, being about the size of the descending colon. It was densely adherent at about the middle of the Psoas muscle. The kidney and ureter were removed in one piece, by means of a combined extra- and intraperitoneal operation.

Abstract from the Pathological Report (No. 3127).

The kidney is altered in shape and is somewhat enlarged, being 13.5 cm. ($5\frac{4}{5}$ inch) long. At the middle of the convex border is a triangular depression, 1.5 x 2.5 cm. ($\frac{1}{2}$ x 1 inch) in size and 5 mm. ($\frac{1}{5}$ inch) in depth, whose base is rough and consists of dense fibrous tissue. The kidney substance itself is rough, presents well-marked lobulation, is slightly granular, and the superficial blood-vessels are dilated. The cortex is dense in consistency, while the pelvis is filled with fluid.

On section, the upper portion is congested, but fairly normal, while at the lower pole the cortical and medullary portions are ill defined and the congestion less marked. Where the depression was noted externally, the renal substance has been replaced by a band of dense fibrous tissue, averaging 5 mm. ($\frac{1}{5}$ inch) in thickness. The pelvis is moderately dilated, its mucosa pale and smooth, except over the apices of the pyramids, where it is much congested.

The ureter is represented by a large, sacculated cylinder, 20 cm. (8 inches) long, and averaging 3 cm. ($1\frac{1}{5}$ inches) in diameter. It is slightly kinked, and contracted at the junction of the first and second quarters, and again at the third and fourth, giving it somewhat the appearance of a string of sausages. The whole is enveloped in a mass of adhesions, containing lobules of fat. On pressure, it is partly fluctuant and partly firm and resistant.

On section, the ureter is of unequal caliber, presenting irregular intervals of dilatation and contraction. The lumen varies from 5 mm. ($\frac{1}{5}$ inch) to 1.5 cm. ($\frac{3}{5}$ inch) in diameter. The walls are greatly thickened and edematous, in some places reaching 1.5

cm. ($\frac{3}{5}$ inch) in thickness. The mucosa is at intervals smooth, at others corrugated. In places it is anemic and thinned out, and in others congested and edematous. The lumen contains a small amount of seropurulent fluid.

Microscopically, the kidney shows the changes commonly seen in advanced, chronic interstitial nephritis. Sections of the ureter show it to be ensheathed in a mass of adipose and newly-formed connective tissue, rich in blood-vessels of moderate size, and showing a general leucocytic infiltration. The walls are greatly thickened, owing in part to hypertrophy of the smooth muscle, but chiefly to a thick tunic of connective tissue, external to the muscular coats. This tissue is very edematous and contains several foci of round cell-infiltration. This coat in places is 7 to 8 mm. ($\frac{1}{3}$ inch) in thickness.

The mucosa lining the canal is also thickened. It presents the usual folds and is covered in general by intact, transitional epithelium. Here and there over the summits of the folds it is thin, sometimes only one layer of poorly staining cells remaining, while at one or two points the surface is denuded of its epithelium. In sections taken at the level of the impacted calculus the lumen is dilated, the folds of the mucous membrane flattened, and the mucosa thinner than elsewhere.

In a few cases, the ureter below the stone has been found stenosed, contracted or converted into a fibrous cord. When the stone is low down there may be prolapse of the ureter into the bladder, as in the case reported by Fenwick (Case 91).

Ulceration of the ureteral wall has occurred, notably in Albarran's case (Case 101), where a stone, located at the pelvic brim had caused a large abscess, pointing below Poupart's ligament.

IV. Symptomatology.

The symptoms of impacted ureteral calculi are very variable. A small stone may pass down the lumen, become lodged in some portion of the canal, and, after the acute colic has subsided, remain quiescent for years without producing any symptoms whatever. This is true provided the stone does not cause the urine to be dammed back.

As pointed out by Tuffier,[4] the acute manifestation, the renal colic, indicates the migration of a calculus, while the cessation of

the pain indicates ordinarily, that the stone has passed on into the bladder, or, more rarely, has become lodged in such a manner that the urine may trickle between the stone and the ureteral wall, the lodged calculus giving no symptoms.

Generally, however, when the foreign body becomes impacted in the canal, it gives rise to symptoms insidious and ill defined. In general, they are the same as those of renal calculus; i. e., pain, tenderness, hematuria, pyuria, anuria or oliguria, and in certain cases, chills and fever, together with a swelling in the flanks.

Pain. The typical pain in this condition is a more or less constant one, described as a dull aching sensation, radiating from a fixed point, downwards along the course of the ureter. This is aggravated at times by attacks of sharp, lancinating pain extending towards the bladder, termed by Tuffier[4] "pseudo-nephritic colic without result." The dull aching pain may be slight and may be increased by flexion of the thigh, the increase being due to the contraction of the Psoas muscle. In the male retraction of the testicle on the affected side may occur.

Tenderness. In a certain number of cases, a fixed point of tenderness can be elicited on deep palpation, at some point along the course of the ureter, at which point a hard nodule may possibly be felt. In a case cited by Morris (Case 70), there had been pain for two months in the right loin, which later became localized at the point where the right ureter crosses the pelvic brim. Here a hard body could be palpated through the abdominal wall. The diagnosis of ureteral calculus was made, and the stone successfully removed by extraperitoneal ureterotomy. In Cabot's case (Case 73) of vaginal ureterotomy, there was localized tenderness, low down in the left inguinal region, and in Case 100 there was extreme sensitiveness on palpating, *per vaginam*, the region of the left ureter.

Hematuria. During the acute stage there is almost always hematuria, caused by the injury done to the ureteral wall. The amount of blood passed varies with the character of the stone, the rough oxalate calculi causing more traumatism than the smooth uric acid stones.

When the calculus becomes impacted, the bleeding may cease or the blood be present only in microscopical amounts. Red blood corpuscles were found microscopically in all four of our

cases. Morris cites an interesting case (Case 51) in which there had been six months of discomfort, aggravated by acute attacks of pain. During these paroxysms, the bleeding was most pronounced. At operation a minute calculus was found, two inches below the renal pelvis. It was very irregular and so firmly fixed by its rough processes that it had to be literally dug out of the ureteral wall.

Pyuria. Pyuria is present when there is an associated pyonephrosis, pyelitis, or cystitis. The amount of pus may in such cases vary greatly, at times being abundant, again only found by the microscopic examination.

Oliguria. The quantity of urine voided in this affection depends upon the condition of the opposite side and the degree of stenosis on the diseased side. In those cases where there are acute exacerbations of pain, the urine is generally diminished in amount at these times, followed in some cases by polyuria. In Mrs. R.'s case, before referred to, and in which a nephro-ureterectomy was done, the urinary history was typical. Mrs. R. volunteered the information that she had voided very small amounts of urine during her attacks of pain and whenever they were unusually severe, the secretion had almost ceased. After a paroxysm, however, the amounts had sometimes been very large, as much as a quart having been passed in a short time.

Oliguria, or the passage of a small amount of urine, is noted in a fourth of the operative cases, and among these there was anuria in sixteen. Inasmuch as many of these reports are very brief, oliguria is probably a much more frequent symptom than these figures would indicate.

Anuria. Anuria is the most dangerous symptom, and the most important indication for operation. The length of time, during which there may be urinary suppression has been variously estimated. Osler[9] states that a person may live from ten days to two weeks with complete suppression. Roberts[10] says that anuria is fatal in from nine to eleven days. Polk's[11] case, in which an only kidney was removed, lived eleven days, while Harrison[12] cites a case of Moxon's, in which there was suppression for fourteen days, followed by the passage of a calculus and subsequent recovery.

The conditions under which a calculus may be present are thus stated by Newman:[13]

1. Reflex inhibition of the function of the opposite healthy kidney.

2. Hydronephrosis or atrophy of the opposite kidney.

3. Tuberculosis, pyonephrosis or congenital absence of the opposite kidney.

4. Bilateral diseases of the kidneys, such as Bright's disease, cystic degeneration, etc.

Of these possibilities, the second most frequently occurs. Legueu[34] in an analysis of 30 cases, found the other kidney atrophic from previous calculous disease, in 20. He found but two instances of fatal anuria where one kidney was sound. Catheterization of both ureters is practically our only resource in clearing up such cases of urinary suppression.

Chills and fever. When the urinary tract, above an impacted stone, is infected, an elevation of temperature, with occasional rigors, is to be expected, although in long standing cases, where there is a free exit for the pus, fever is not always present.

Tumor in the flank. The presence of a persistent tumor in the region of the kidney has been noted in nine cases. This, however, by no means represents the frequency of nephrectasis, for the pelvis of the kidney may be considerably dilated without the distention becoming apparent on palpation. An intermittent tumor in the flank has been present in a few cases, but is more frequently present in other conditions, such as stricture of the ureter, floating kidney with ureteral kinks, and pressure on the ureter from without, as by uterine tumors. The patient, Miss K., in whose right ureter two stones were found, had herself noticed a swelling in the right renal region, which appeared and disappeared at intervals. Associated with this was the passage of correspondingly large or small amounts of urine.

Vesical symptoms. When a calculus is located high up in the ureter, there are seldom any signs of irritability of the bladder, such as vesical tenesmus, painful or frequent micturition; although Lange (Case 12) and Guyon (Case 21) have each reported instances in which the stone was found within an inch of the pelvis of the kidney, and the principal symptom was difficulty in urination. With a stone high up and an irritable bladder, there is usually an associated cystitis.

On the contrary, a calculus located low down, near the vesical

orifice of the ureter, may produce as its only symptoms, those of cystitis or stone in the bladder. Such cases are reported by Emmet (Case 71), Doyen (Case 76), Czerny (Case 93), Whitehead (Case 95), and others. We then have vesical spasm, frequent and painful micturition, dragging pain in the hypogastrium, and perhaps hematuria.

V. Diagnosis.

The diagnosis of calculous stenosis of the ureter is by no means easy. It must be made from the history and from the information derived from the physical examination of the patient, supplemented by special methods of research, such as cystoscopy, catheterization of the ureters, and radiography..

This affection is to be suspected when a patient gives a history of repeated attacks of renal colic, occurring at intervals for years, and although the attacks have usually terminated with the passage of a calculus and the cessation of symptoms, the last one ended more slowly and left behind a constant dull aching pain, with possibly tenderness somewhere along the course of the ureter. Such is a typical history. Generally, however, the symptoms are so variable and resemble so closely those of nephrolithiasis, that it is only in rare cases that the diagnosis can be made from the history.

Physical examination of the patient is often negative, but the following points must be kept in mind and carefully searched for.

(1). *Signs of enlarged kidney.* On inspection there may be bulging in one or the other flank, the swelling proceeding from beneath the costal margin and extending toward the median line. On bimanual palpation, one hand being placed behind the floating ribs and the other on the hypochrondriac region in front, the tumor is found to occupy the flank, to be somewhat movable, and if large, to give the sensation of fluctuation. It is often tender to the touch. On percussion the swelling is dull, the dulness being directly continuous with the normal kidney dulness, found behind, between the ninth and eleventh ribs, in the scapular line.

(2). *Tenderness at some point in the course of the ureter.* The course of the abdominal portion of the ureter is marked externally by a perpendicular line drawn upward from the middle of Poupart's Ligament, and it is along this line that deep pressure should

be made in the palpation. In a few cases, notably those reported by Tuffier (Case 18), Desguin (Case 64), and Morris (Case 70), there has been a point of tenderness at some level along this line. In Morris' case he felt a distinct, hard body, which proved to be an impacted calculus. It is only in very thin patients, with lax abdominal walls, that one can hope to palpate an ureteral calculus in the abdominal examination.

(3). *Rectal or vaginal palpation.* When the stone is located within five centimeters of the vesical orifice, it can be felt bimanually through the rectum or vagina. One of the first diagnoses of this condition to be made during life, was that of Dr. Rawdon,[15] who, in 1879, detected, by rectal palpation, a stone in the ureter of a twelve-year old boy. The diagnosis was confirmed *post mortem.* Grube and Resinkoff[16] do not hesitate, in making this examination, to introduce the whole hand into the rectum, the latter advocating the use of the left hand, because it is smaller.

In palpating the ureter through the vagina, one begins about two centimeters in front of and to the side of the cervix uteri, and then makes pressure upwards and outwards in the vaginal fornix, pressing the mucous membrane of the vagina hard against the pelvic wall. In this way, even a slight thickening of the ureter can be made out, and any hard body, such as a stone, readily felt.

The examination of the urine, microscopically, is of the greatest importance in making the diagnosis of calculous disease, but the urine in cases of ureteral stone has no distinguishing characteristics. Red blood corpuscles should be carefully searched for, as well as the crystals of uric acid, calcium oxalate, and the triple phosphates.

While these general methods of examination are very important, and may in rare cases lead to a positive diagnosis, it is by means of special procedures that the most aid is obtained. These special procedures are radiography, cystoscopy, and the catheterization of the ureters.

Radiography. The possibilities of exact diagnosis by means of the Roentgen rays, are well shown by the excellent work of Leonard,[17] who, with others, has opened a large field of research, which, with more exact methods and increased accuracy of interpretation, promises much.

Cystoscopy. An examination of the bladder by means of the

Caspar or Nitze cystoscope in the male, or by the open speculum and air distended bladder in the female, is of the greatest importance.

It establishes at the outset the presence or absence of cystitis, and clears up at once those cases in which a stone is impacted in the mouth of the ureter and projects into the bladder. Hall (Case 97), thus discovered, in the ureteral orifice, a calculus, which he was able to remove with a searcher, introduced through the cystoscope. Young (Case 99) has also accomplished the same result by means of an ureteral catheter, introduced through a Caspar cystoscope. The patient was a male, aged 31, who had suffered from renal colic for seven years, and came to the clinic with acute suppression of urine. On introducing the cystoscope, a small stone was plainly seen in the ureteral orifice, and readily dislodged by a catheter.

The appearance of the ureteral orifices has considerable significance. Thus in Dr. Kelly's fifth case (Case 100), in which a stone was situated in the vesical portion of the ureter, the orifice appeared broad and pouting and was surrounded by a deeply reddened mucosa, extending from 4 to 6 mm. on all sides of the opening. This angry appearance plainly indicated the affected side, but the orifice was not found to be dilated, as was at first surmised. On the contrary, it was contracted and strictured, the eversion being somewhat analogous to the everted cervical mucosa sometimes seen in endocervicitis. This appearance of irritation around the orifice may also be present in any affection of the ureter, such as tuberculous ureteritis or pyoureter, from any cause. In Fenwick's case (Case 91), in which a stone was removed from the lower end of the ureter by a perineal incision, the cystoscopic examination revealed a prolapsed ureter, surrounded by a villous growth.

Guyon[18] has called attention to sensitiveness of the lower part of the ureter, elicited by the rectal touch, as a symptom of many ureteral affections. This should be tested with a searcher introduced through the cystoscope. It was present in a marked degree in the case just referred to.

Catheterization of the ureters. No other procedure gives as much information in regard to this condition as does the introduction of catheters carrying wax tips, into the ureters. It not

only establishes beyond doubt the presence of a stone, but it locates it exactly, tests the efficiency of the supposedly sound side, and procures fresh, uncontaminated urine for microscopic and bacteriologic examinations.

The ureteral catheter should be of the yellow silk variety, about 2 mm. in diameter, having a conical tip and lateral eye. These may be sterilized by boiling for two minutes, without deterioration.

The best mixture for covering the tip consists of dental wax, two parts, and olive oil, one part. This is kept in a short test tube, is sterilized in the autoclave, and when needed for use is readily melted over an alcohol flame. The tip is prepared by dipping the conical end of the catheter, for a distance of 3 or 4 mm., into the melted wax, quickly withdrawing it, and allowing it to cool, while hanging downward. The resulting ball of wax should be examined with a lens to make certain that it is perfectly smooth.

After locating the orifice, the catheter is introduced into the ureter, care being taken that the polished tip rubs against nothing during the manipulation. By gently pushing the catheter up the ureter, the slightest obstruction is readily appreciated, and if due to an impacted stone, scratch marks on the smooth wax will almost surely be found. The secreting power, if any, of the kidney, is estimated, urine is collected for examination, and cultures are obtained, before the catheter is withdrawn.

In three of the four cases of ureteral stone which have occurred in the gynecological department of the Johns Hopkins Hospital, a positive diagnosis has thus been made and the exact location of the stone established. Dr. Kelly has also had one additional case (Case 100), while Russell demonstrated the value of the procedure in Case 60.

Differential Diagnosis.

Impacted ureteral calculus has to be diagnosticated from—

(1). *Renal calculus.* As has been stated, the symptoms of ureteral calculus are very frequently indistinguishable from those of stone in the pelvis of the kidney, and in a considerable number of the cases in which the localization was high in the ureter, the stone has only been discovered after an exploration of the kidney, undertaken with the belief that the calculus was a renal one.

Persistent abdominal pain, located in a small area, with a point of tenderness somewhere in the course of the ureter, may cause a suspicion that the stone is an ureteral one, for the classical pain of renal calculus is one situated in the loin, with tenderness in the side, below the eleventh or twelfth rib. While the symptoms and the general examination furnish at best only a probable diagnosis, the method of ureteral catheterization, with the wax-tipped bougie and radiography, give us exact information, both as to the presence of a stone and its precise location.

(2). *Vesical calculus.* In those cases in which the stone is impacted close to the vesical opening, the symptoms simulate very closely those of stone in the bladder. Such was the case in the instances reported by Emmet (Case 71), Richmond (Case 94), Czerny (Case 93), Helferich (Case 86), Doyen (Case 76), and others. A cystoscopic examination will differentiate a stone protruding from the ureteral opening, or a calculus lying free in the bladder.

It has been a much mooted question as to whether many of the cases reported as stones encysted in the bladder, were not in reality stones caught in that part of the ureter which traverses the bladder wall. If the ureteral opening be not patent and a bulging be seen in the location of the opening, the diagnosis of ureteral calculus would seem probable, whereas the bulging being elsewhere in the bladder the probability would be a stone encysted in a saccule of the vesical mucosa.

(3). *Movable kidney.* While movable kidney may be associated with attacks of violent abdominal pain, nausea and vomiting, chills and fever, and finally collapse—the crises described by Dietl in 1864—a careful examination of the urine, which in these cases is normal, together with the physical examination of the patient, will generally serve to distinguish this from calculous disease, either of the kidney or ureter. In doubtful cases, ureteral catheterization must be resorted to.

(4). *Cystitis.* Vesical irritation, with frequent and painful micturition, occurs in those cases of stone situated in or just above the mouth of the ureter. These symptoms may occur, although no inflammation of the vesical mucosa be present. A cystitis, however, frequently exists. The examination of the urine is of considerable aid in differentiating a cystitis, although the importance

of this, especially the reaction of the urine, has been greatly overestimated. One frequently sees in text-books and monographs on affections of the urinary tract, the statement that the urine in cystitis is alkaline, while that secreted in renal and ureteral affections is acid. As has frequently been demonstrated in our clinic, the reaction of the urine in cystitis depends solely upon the organism present as the etiological factor.

A stone located in the lower end of the ureter, can usually be felt by the bimanual examination, through the rectum or vagina.

(5). *Ureteritis.* Inflammation of the ureter is most frequently of the tuberculous type, and in this affection the nodules which are sometimes produced, might be mistaken for calculi impacted along the course of the tube. The thickened and enlarged ureter can be felt by bimanual palpation. The finding of tubercle bacilli either in the mixed urine or in that separated from the affected side, will clear up the diagnosis.

(6). *Stricture of the ureter.* Stricture of the ureter may follow an old infection or a recent trauma. If the ureter be catheterized, the bougie will be felt to be grasped and then, if it be not too tight, pass by the stricture. A stone may be lodged above the stenosed point, in which case scratch marks will be found on a wax tip.

(7.) *Neoplasms of the bladder.* A new growth in the vesical wall may be so situated as to occlude the opening of one or the other ureter, thus causing symptoms possibly to be confounded with calculous stenosis. Voeleker has reported a case in which the lower two inches of the ureter were occluded by a primary carcinoma. The cystoscope and ureteral catheter will serve to differentiate such cases.

(8). *Diseased appendages.* A stone low down in the ureter might be mistaken for a prolapsed and adherent ovary. On vaginal examination, it should be distinguished by its consistency, mobility and position. In the case of a calculus the mass felt would be hard, easily moved in the loose cellular tissue, and located either beneath the mucosa of the lateral fornix, or that of the anterior-lateral vaginal wall. Its long axis would be in the direction of the ureter. An ovary, while firm, would not be as hard; it would be more firmly fixed, and would be located either in Douglas' sac or behind one or the other broad ligament. In the

latter case the amount of tissue between it and the examining finger would be greater than in the case of a calculus. Cullingworth's (Case 61) intraperitoneal ureterotomy was done in a case which had been diagnosticated as pyonephrosis and independent ovarian disease. The vaginal examination showed hard masses to the right and left of the uterus, while the laparotomy revealed a stone in the right ureter, just above the bladder.

Conditions which may more rarely cause a mistake in the diagnosis, when the symptoms are on the right side, are gall-stone colic and appendicitis. The urinary examination in such cases is of help. Red blood corpuscles should be searched for microscopically. Tuffiier[18] has shown by means of radiographs that the ureter passes directly through McBurney's point, although at a different level, and points out that a stone at this level and a concretion in the appendix would give similar shadows. In one case, Tuffier made the diagnosis of ureteritis, probably of calculous origin, in a patient with a family history of renal colic, who had had severe pain along the line of the right ureter, associated with oliguria. At operation an appendicial abscess, situated high up behind the colon, was found.

In Desguin's case (Case 64), that of a man thirty-four years of age, there was a history of abdominal pain for twenty-nine years, with a fixed point of tenderness just above McBurney's point. The diagnosis between ureteral calculus and chronic appendicitis was not made, but the operation revealed a stone impacted at the brim of the pelvis.

VI. Treatment.

The treatment naturally divides itself into (1) medical, and (2) surgical.

The medical treatment is that laid down for nephrolithiasis, in which dietary measures and the free use of mineral waters are the chief indications. Massage along the course of the ureters has been successfully employed in one case reported by Byford,[19] and electricity has been used with the hope of setting up contractions of the ureter and thus causing the stone to be expelled. Casper has recommended the catheterization of the ureter and injection of sterilized sweet oil at the level of the impaction, a procedure much more rational than that proposed by Reginald Harrison,[20] of filling

the bladder with a bland solution under pressure, with the idea of dilating the ureter and favoring the passage of the stone. On account of the valve-like action of the ureteral opening, it is impracticable to force fluid up the ureter; indeed, Young has shown that this is quite impossible in the cadaver.

The treatment of this condition is mainly surgical and the particular operation selected will, of course, vary according to the probable location of the calculus.

When the stone is seen projecting from the ureteral orifice into the bladder, it may be removed through the cystoscope, as was done by Hall (Case 97), who dislodged a stone thus located, by means of the ureteral searcher, forcing it into the bladder, from which it was readily removed. The stone in Young's case (Case 99) was also removed in this way.

We have seen that in 56 per cent of the cases operated upon, the stone was located within 6 cm. of the vesical orifice. In many of these, the calculus was lodged in the vesical portion of the ureter (that part of the tube, about three quarters of an inch in length, which traverses the bladder wall). When the diagnosis of such a localization is made, one should attempt, in the female, to dilate the lower end of the ureter with the ureteral dilators. In this way the caliber of the tube may be increased sufficiently to allow of the passage of the concretion. This procedure can be carried out under cocaine anesthesia, as was done in Case 100.

The patient, a woman aged thirty-eight years, was suffering from pain in the left kidney, extending down the left ureter to its vesical orifice, at which point the distress seemed to be centered.

By the vaginal examination, an apparently normal right ureter was found, while that on the left side was exquisitely sensitive. A distinct, firm, enlargement was felt about half way between the internal urethral orifice and the cervix uteri. At this point the patient located her greatest suffering and was unable to bear more than the slightest pressure.

To prove the presence of a calculus at this point, Doctor Kelly cocainized the tissues by injecting 6 cc. of a 1% solution, by means of a long hypodermic needle thrust directly through the vaginal wall into the tender spot felt *per vaginam*.

The cystoscope was then introduced into the bladder, which everywhere appeared normal, except at the left ureteral orifice,

where the mucous membrane was reddened and inflamed. A wax-tipped catheter, prepared as stated above, was then inserted into the ureter, and on removal distinct scratch marks were found.

By means of the ureteral dilators the opening was stretched until it admitted a sound 3 mm. in diameter. Nineteen hours later, the patient passed a stone 10 by 3 mm. in size.

Another method of enlarging the ureteral orifice is to slit the mucous membrane. This can best be done by means of the alligator scissors.

In the male the dilatation is more difficult. If it is impossible, a stone in this situation can be removed either by suprapubic or perineal lithotomy. The former is to be preferred, on account of the depth of the perineal wound and the difficulty of exposing the ureter through the lower incision.

When the calculus can be felt *per vaginam*, but is too high to be removed through the urethra, it may be reached by means of a vaginal incision, *vaginal ureterotomy*. An incision is made through the vaginal wall and the finger worked upward into the loose areolar tissue, which underlies it. The hand of the assistant, pressing down from above, fixes the stone, while the operator makes a longitudinal incision through the ureteral wall, with sharp pointed scissors. The alligator scissors greatly facilitate this step in the operation. All incisions into the ureter should be longitudinal, as it has been shown that longitudinal wounds of the ureter, as those of the urethra, close without impairing the lumen of the tube. After the calculus has been removed with the stone forceps, a small gauze drain should be inserted, with the object of keeping the incision in the vaginal wall open until that in the ureter closes.

In Case 84 Doctor Kelly removed, by the vaginal route, a stone situated in the right ureter, 6 cm. from the vesical opening. This calculus could not be felt bimanually, but had been demonstrated both by the wax-tipped catheter and by the Roentgen rays. Before going in below, a median abdominal incision was made and the stone exactly located. At first it did not seem possible to reach it through a vaginal incision, but by pushing it down and fixing it, it could just be touched with a finger in the vagina. While an assistant held it in this position, Doctor Kelly made an incision in the vault of the vagina, opened the ureter with the alligator scis-

sors, and removed the calculus with stone forceps. A catheter was left in the ureter, projected through the bladder and urethra, and a small gauze pack placed in the vaginal wound. There was no leakage until the gauze was removed on the tenth day, when there was considerable urinous discharge, *per vaginam*, for a few days, the fistula, however, gradually contracting down and closing completely on the fifteenth day.

The calculus having been demonstrated to be at or a little below the pelvic brim, an incision similar to that employed for tying the iliac artery, is recommended. Approaching the peritoneum from behind, the ureter is searched for in its superior layer. Having located the obstruction, a longitudinal opening is made into the ureter, the stone extracted, and the ureteral wound closed with interrupted fine silk sutures. In placing these stitches, great care must be taken not to encroach upon the lumen of the ureter, as such nonabsorbable material may give rise to the formation of a primary ureteral concretion. A small gauze drain should be inserted and the remainder of the wound closed. In case the wound is too deep to permit the placing of the sutures, a drain is inserted. These ureteral wounds practically always heal.

On account of the difficulty, or in some cases the impossibility, of reaching the lower three or four inches of the ureter from in front by an extra-peritoneal incision, Cabot[21] has devised an incision modified from that employed by Kraske for excision of the rectum. Cabot finds "that an incision along the border of the sacrum, on the side upon which it is wished to reach the ureter, stopping just below the point of the coccyx, with a division of the sacro-iliac ligaments and the removal of the coccyx and the lower part of that side of the sacrum, lays open the pelvic cavity in a most satisfactory way, and gives easy access to the lower three or four inches of the ureter. The only difficulty in this dissection is in finding the ureter, which in its collapsed state cannot be easily made out." So far as I know, this apparently excellent operation has never been employed.

To reach the abdominal portion of the ureter, two routes are possible, trans- and retroperitoneal. Of these the latter should always be chosen, unless some co-existing condition is suspected, calling for a laparotomy. The extraperitoneal route is to be preferred, first on account of the danger of infecting the peritoneum,

and second, because of a less troublesome and dangerous sinus, should one persist. The incision from behind has been well described by Israel.[3] Israel's incision begins at the junction of the erector spinæ muscles and the twelfth rib, extends downward and forward until sufficiently large to allow the kidney and upper part of the ureter to be drawn out. In order to reach the ureter lower down, this incision is continued downward toward the middle of Poupart's ligament, where it turns mesially and extends to the outer border of the rectus muscle.

The most perplexing step in the operation is to find the ureter. In making a number of dissections, Cabot found that the ureter always strips up with the peritoneum, on account of bands of fibrous tissue which bind it to that membrane; and, furthermore, that "the relation of the ureter to that part of the peritoneum which becomes adherent to the spine is, within a slight range of variation, pretty constant, the ureter lying just outside the line of adhesion. So that if the surgeon has stripped up the peritoneum and come down to that point where it refuses to strip readily from the spinal column, he will find the ureter upon the stripped up peritoneum, at a short distance outside of this point."

When the stone has been located, an attempt should be made, as recommended by Tuffier and Israel, to push it up into the renal pelvis, from which it may be more readily removed. In many of the cases where the calculus is within five or six centimeters of the pelvis, this is possible, especially if a moderate degree of dilatation exist above the stone. If it cannot be moved, an incision must be made longitudinally over the concretion, the wound later being closed with fine silk sutures. Every case should be drained, to guard against leakage.

VII. Prognosis.

The prognosis as regards the life of the patient without operation depends very largely upon the condition of the opposite kidney. If that be unimpaired, it undergoes a vicarious hypertrophy and then, though the diseased side atrophies completely and becomes worthless, there may be many years of excellent health. Such patients, however, are always in danger of subsequent calculous disease on the side remaining functional, this occurring in about 50% of the cases. Anuria with subsequent uræmia is then the terminal affection.

The complication most to be feared is an ascending infection from the bladder, causing a pyoureter or pyonephrosis. Unless surgical treatment is resorted to, this is an ever present menace to the life of the patient.

Of the 101 cases operated upon, 21 have died, making a mortality of 20.8 per cent.

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4. Tuffier. Loc. cit.
5. Kelly. Operative Gynecology, Vol. I, p. 449.
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18. Guyon. Loc. cit. Case 21.
19. Byford. Am. Jour. Obst., 1889, Vol. XXII, p. 963.
20. Harrison. Lancet, March 10, 1888.
21. Cabot. Am. Jour. Med. Sciences, Vol. CIII, p. 43.

	Reference.	Sex and Age.	Chief Symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
A1 1.	Morris. Hunterian Lectures, 1898, p. 184.	Male, 38.	6 yr., pain, pyuria and passage of stone.	Left, 2 in. from lower end.	Not stated.	Left lumbar nephrectomy.	Death 2nd day.
2.	Briddon. N. Y. Med. J. 1890, I, p. 583.	Male, 15.	3 wk., abdom. pain, nausea and vomiting	Not stated.	Not stated.	Left lumbar nephrectomy.	Death 7th wk. Double ureter.
3.	Lloyd. Br. M. J. 1896, II, p. 1206.	Male, 37.	21 yr., attacks pain left side. Hematuria	Lower end ureter. *Post mortem.*	Size of horse bean.	Left lumbar nephrectomy.	Death 64 hrs.
A2 4.	Richardson. Bos. Med. & S. J. 1893, I, p. 359.	Female, 33.	1 yr., abdom. pain. Tumor left side.	Lower end, one side of double ureter.	Not stated.	Abdominal nephrectomy.	Recovery.
B 5.	Postnikow. Arch. f. kl. Chir., 1895, 49, p. 675.	Female, 55.	Painful tumor in loin.	Lower end left ureter. Felt *per vaginam.*	14 stones, largest 11 x 19 mm.	Nephro-ureterectomy.	Recovery.
6.	Salin. Jahr. Geburtsh. u. Gyn. 1896, p. 319	Not stated.	Not stated.	Lower part ureter.	Not stated.	Nephro ureterectomy.	?
7.	Willy Meyer. Jacobi Festschift, 1900.	Male, 23.	Renal colic 5 yr. before. Hematuria. Pyuria.	Vesical end of ureter	Size of large pea.	Lumbar nephrectomy. 15 mo. later, ureterectomy.	Recovery.
8.	Israel. Klinik der N'Krandheiten, p. 372.	Male, 33.	9 yr., attacks pain in left side. Hematuria	Pelvic portion of ureter. Felt *per rectum.*	Length 17 cm. Circum. 9 cm.	Nephrectomy. 1 mo. later, ureterectomy	Recovery.
9.	Israel. Ibid, p. 374.	Male, 39.	2 yr., pain left side, nausea and vomiting	Vesical portion of ureter. Felt *per rectum.*	Wt. 12.2 gms. Cal. phosphate.	Nephrectomy. 1 mo. later, ureterectomy.	Recovery.
10.	Israel. Ibid, p. 375.	Female, 27.	2 yr., pain in left side. Passage calculi	Pelvic portion of ureter. Felt *per vaginam.*	Blood corpuscles, salts of calcium, uric acid.	Nephro ureterectomy.	Recovery.
11.	Kelly. J. A. M. A., May 11, 1901.	Female, 29.	3 yr., renal colic. Oliguria.	3 cm. above bladder in left ureter.	Ovoid, rough, 3 x 1.5 x 1.3 cm.	Nephro-ureterectomy.	Recovery.

	Reference.	Sex and Age.	Chief Symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
C1 12.	Lange. Med. News, 1886, I, p. 69.	Male, 30.	18 yr., pyuria and frequent micturition.	1 in. below pelvis in right ureter.	Fibrinous clot with many small stones.	R. lumbar nephrotomy.	Recovery.
13.	v. Bergmann. Ber. klin. W. 1887, p. 777.	Male, 54.	9 yr., renal colic. Anuria for 6 days.	6 cm. below pelvis in right ureter.	Not stated.	R. lumbar nephrotomy.	Recovery.
14.	Israel. Deut. med. W., 1888, p. 4.	Male, 49.	Renal colic. Anuria for 6 days.	10 cm. below pelvis in left ureter.	Not stated.	L. lumbar nephrotomy. Stone pushed up.	Death 6th day.
15.	Torrey. Am. J. Med. Sc. V. 97, p. 579.	Female, 47.	5 yr., renal colic. Pyuria. Uraemia.	1 in. below pelvis.	Like olive stone, $\frac{7}{8} \times \frac{1}{2}$ in.	L. lumbar nephrotomy.	Recovery.
16.	Lucas. Br. M. S. 1891, I, p. 115.	Female, 37.	17 yr., hematuria. Pain in R side.	Upper end of ureter. Acted as ball valve.	$\frac{3}{4} \times \frac{3}{4}$ in.	Left lumbar nephrotomy.	Recovery.
17.	Duffau-Largarosse. Ann. d. mal. d. Org. G. U., Jan., 1892.	Male, 59.	3 wk., pain right side. 8 days anuria.	Lower part right ureter.	Size of grain of rice.	Right lumbar nephrotomy.	Died.
18.	Tuffier. Ibid, 1893, p. 693.	Male, 41.	8 yr., attacks of renal colic. Tenderness along ureter.	At prom. of sacrum.	Ovoid, 2 x 3 cm. Uric acid.	Right lumbar nephrotomy.	Recovery.
19.	Kadian. La Med. Moderne, 1894, vol. V, p. 1076.	Female, 58.	Tumor in left flank. Anuria.	Both ureters plugged.	In right, 2.5 cm. long. In left, smaller.	Left lumbar nephrotomy.	Death 8 hrs.
20.	Legueu. Ann. d. mal. d. Org. G. U., 1894, p. 696.	Male, 65.	Renal colic. Vomiting. Anuria 5 days.	Just below pelvis.	Conglomerate mass of uric acid stones.	Left lumbar nephrotomy. Stone pushed up.	Recovery.
21.	Guyon. Ibid. 1894, p. 355.	Female, 35.	6 yr., left renal colic. Hematuria. Pyuria.	Just below pelvis.	Cylindrical, 53 x 11 mm.	Left lumbar nephrotomy. Stone pushed up.	Recovery.

	Reference.	Sex and Age.	Chief Symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
22.	Legueu. Ibid. 1895, p. 865.	Male, 47.	Symptoms of stone in kidney. 6 days anuria.	Upper end of ureter.	Not stated.	Lumbar nephrotomy	Recovery.
23.	Legueu. Ibid.	Male, 54.	Symptoms of stone in kidney. 6 days anuria.	Upper end of ureter.	Not stated.	Lumbar nephrotomy	Died.
24.	Israel. Ber. klin. Woch ensch 1896, p. 841.	Female, 45.	9 yr., left renal colic. 3 yr., right renal colic.	At pelvic brim. Sounding ureter from above.	Not stated.	Left lumbar nephrotomy. Stone pushed up.	Recovery.
25.	Fenger. Am. J. Med. Sc. 1896, 112, p. 667.	Female, 32.	10 yr., attacks of renal colic. Tumor in right flank.	$2\frac{1}{2}$ in. below pelvis. Sounding ureter from above.	4 stones.	Right lumbar nephrotomy. Stone pushed up.	Recovery.
26.	Morris. Loc cit. p. 278.	Female, 35.	Pain in left side. Two previous operations on right kidney.	Upper end of left ureter.	Not stated.	Left lumbar nephrotomy. Stone pushed up.	Died 2 hrs.
27.	Tuffier. Loc. cit. 1898, p. 992.	Male, 32.	14 yr., renal colic. Hematuria.	Upper end of ureter.	Uric acid surrounded by blood clot.	Lumbar nephrotomy	Recovery.
28.	Israel. Klinik der N'Krankheiten, p. 363.	Male, 60.	Pain in left side for several years.	Vesical portion. Discovered *post mortem*.	Size of 3 millet seeds. Calcium oxalate.	Lumbar nephrotomy	Died.
29.	Israel. Ibid. p. 364.	Male, 64.	2 yr., abdom. pain. Later left lumbar pain.	Vesical portion. Discovered *post mortem*.	Spindle shape. 1.25 cm. long.	Nephrotomy.	Died.
30.	Israel. Ibid. p. 370.	Female, 42.	5 yr., attacks renal colic. Nausea and vomiting.	Pelvic portion of ureter.	Round, smooth. Wt. .9 gm.	Nephrotomy. Stone pushed up.	Died.
31.	Israel. Ibid. p. 371.	Female, 40.	9 yr., attacks renal colic. Pyuria.	Near bladder. Felt *per vaginam*.	Stone enveloped in a membrane.	Nephrotomy. Stone pushed up.	Recovery.
32.	Hall. Med. Rec., 1890, 38, p. 630.	Female, 36.	4 yr., nephritic colic.	3 in. below pelvis, left ureter. Exploratory laparotomy.	Horseshoe shape. $\frac{5}{16} \times \frac{5}{16}$ in.	Laparotomy for diagnosis. Nephrotomy. Stone pushed up.	Recovery.

	Reference.	Sex and Age.	Chief Symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
33.	Perkins. Ann. of Surg., 1898. Vol. 27, p. 643.	Female, 10.	Injury to right side, followed by severe pain.	At pelvic brim. Exploratory laparotomy.	¾ in. long. Size of lead pencil.	Laparotomy for diagnosis. Nephrotomy. Stone pushed up.	Recovery.
D 34.	Bardenhauer. Cent. f. Chir., March 25, 1882.	Female, 27.	6 yr., pain in left side. Abscess opened. 2 days anuria.	Upper end of left ureter.	Bean size.	Extraperitoneal ureterotomy. Suture.	Recovery.
35.	Lister. Godlee. Practitioner, 1887, p. 251.	Male, 31.	10 yr., renal colic. Pyuria. Large abscess opened.	1 in. above crest of ilium.	Size and shape of small almond.	Extraperitoneal ureterotomy. No sutures.	Recovery. Fistula.
36.	Ralfe and Goolee. Lancet, 1889, I, p. 428.	Female, 26.	4 yr., renal colic. Anuria 53 hrs.	2 in. below kidney.	Not stated.	Extraperitoneal ureterotomy. No sutures.	Recovery.
37.	Kirkham. Ibid. 1889, I, p. 525.	Male, 58	6 yr., renal colic. Anuria 6 days.	½ in. above crossing iliac artery.	Size and shape of date stone.	Extraperitoneal ureterotomy. No sutures.	Recovery.
38.	Cabot. Bos. M. & S. J., 1890, p. 247.	Male, 40.	6 yr., renal colic. Fever. Nausea. Vomiting.	2 in. below kidney, in left ureter.	Wt. 2 grains.	Extraperitoneal ureterotomy. No sutures.	Recovery.
39.	Twynam. Br. Med. J., 1890, II, p. 648.	Male, 8.	16 mo., pain in left side. Hematuria. Pyuria. Fever.	2 in. above bladder in right ureter. Laparotomy 3 wks. previously.	Wt. 6 grains.	Extraperitoneal ureterotomy. Suture.	Recovery.
40.	Fenger. Chic. Med. Recorder, Mch., 1893.	Male, 35.	2 yr., renal colic.	1½ in. below kidney.	2 stones.	Extraperitoneal ureterotomy No sutures.	Recovery.
41.	Morrison. Lancet, 1894, II, p. 1093.	Male, 46.	4½ yr., renal colic. Passage 2 stones.	1 in. above bladder.	2 stones. Larger size of filbert.	Extraperitoneal ureterotomy. Suture.	Died on table.
42.	Morrison. Ibid.	Male, 31.	9 yr., renal colic. Tenderness along ureter.	3 in. below pelvis. Sounding ureter from above.	Not stated.	Extraperitoneal ureterotomy. No sutures.	Recovery. Fistula 4 mo.

	Reference.	Sex and Age.	Chief Symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
43.	Hind. Br. Med. J., 1894, I, p. 960.	Male, ?	7 days., anuria without symptoms.	Upper part ureter.	$\frac{1}{2} \times \frac{1}{16}$ in.	Extraperitoneal ureterotomy. No sutures.	Died 58 hrs.
44.	Cotterell. Ibid. 1894, I, p. 1022.	Female, 61.	Renal colic. 2 previous operations. No stone found.	Just below brim of pelvis.	Wt. 4 gms.	Extraperitoneal ureterotomy. No sutures.	Recovery.
45.	Pousson and Demons. Ann. d. mal. d. org. G. U., 1894, p. 99.	Male, 43.	Several years, renal colic, both sides. Passage calculi, 9 days. Anuria.	Few cm. below pelvis.	Size of bean.	Extraperitoneal ureterotomy. No sutures.	Death 24 hours.
46.	Briddon. Ann of Surgery, 1895, I, p. 29.	Male, 49.	44 yr., left renal colic 4 yrs. previously, nephrotomy. No stone found.	Just below brim of pelvis.	Oval, 2 x $1\frac{1}{2}$ in.	Extraperitoneal ureterotomy. No sutures.	Recovery.
47.	Israel. Ber. klin. Woch. 1896, p. 841.	Male, 52.	4 yr. Renal colic. 6 days anuria.	5 cm. below pelvis. Sounding from above.	Size of cherry stone.	Extraperitoneal ureterotomy. No sutures.	Recovery.
48.	Robinson. Br. Med. J., 1897, II, p. 648.	Female, 23.	8 yr., renal colic. Hematuria. Tumor right side.	$\frac{1}{4}$ in. from bladder. Ureter catheterization. Felt *per vaginam*.	$1\frac{1}{2} \times \frac{1}{2}$ inch. Ox alates and uric acid and phosphates.	Extraperitoneal ureterotomy, Suture.	Recovery.
49.	Robinson. Lancet, 1898, I, p. 508.	Female, 16.	10 yr., renal colic. Hematuria. Tumor left side.	Level of cervix uteri. Felt *per vaginam*.	$\frac{5}{8} \times \frac{3}{8}$ inch. Calcium oxalate.	Extraperitoneal ureterotomy, Suture.	Recovery.
50.	Morris. Loc. cit. Table II, No. 44.	Male, 31.	7 yr., renal colic. Hematuria. Passage stones.	4 in. below pelvis.	Not stated.	Extraperitoneal ureterotomy.	Recovery.
51.	Morris. Lancet, 1899, II, p. 1652, Case 37.	Female, 33.	Pain in right loin. Hematuria marked.	2 in. below kidney. Sounding from above	Calc. ox. Rough, adherent to ureteral wall.	Extraperitoneal ureterotomy. 1 suture.	Recovery.
52.	Freyer. Lancet, 1899, I, p. 211. Tran. M. Soc. London, 1899	Male, 23.	19 mo., renal colic. Tumor in right side.	4 in below kidney Sounded from above.	Not stated.	Extraperitoneal ureterotomy. No sutures.	Recovery.

	Reference.	Sex and Age.	Chief symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
53.	Clark. Ibid.	Female, ?.	2 yr., renal colic.	5 in. below kidney. Sounded from above.	Not stated.	Extraperitoneal ureterotomy. No sutures.	Recovery.
54.	Keen. J. Am. Med. Ass. 1901, 37, p. 567.	Male, 10.	8 yr., pain in right side. Hematuria.	Just below brim of pelvis. Skiagraph.	1.5 x 1. x .8 cm. Cal. phosphate.	Extraperitoneal ureterotomy. Suture.	Recovery.
55.	Israel. Loc. cit. p. 367.	Female, 24.	2½ yr., dysuria. Pain in side.	Below prom. of sacrum. Felt *per vaginam*.	4.77 gms. Ca. and Mg. phosphate.	Nephrotomy. Extraperitoneal ureterotomy. Suture.	Recovery.
56.	Israel. Loc. cit. p. 368.	Female, 24.	15 yr., pain in right side. Dysuria.	Pelvic portion of ureter.	1.43 gms. Cal. oxalate.	Nephrotomy. Extraperitoneal ureterotomy. Suture.	Recovery.
57.	Israel. Loc. cit. p. 369.	Male, 31.	6 yr., right renal colic. Ureter painful on pressure *per rectum*.	Vesical portion. Sounded from above.	Small oval. Cal. ox. and phos.	Nephrotomy. Extraperitoneal ureterotomy. Suture.	Died.
58.	Young. Am. Med., 1902, IV, p. 209.	Male, 29.	27 yr., attacks renal colic. Vesical pain radiating to penis.	Juxta-vesical portion Ureteral catheterization. Radiograph.	Smooth, oval. 2 x 1.5 x 1 cm.	Extraperitoneal ureterotomy. No sutures.	Recovery.
59.	Finney. Ref. Young, Ibid.	Male, 33.	10 yr., renal colic. Attacks of pain beneath Poupart l'g't.	Para ischial portion of ureter. Radiograph.	3 calculi. Each about 1.5 x 1 x 1 cm.	Extraperitoneal ureterotomy. Suture.	Recovery.
60.	Russell.	Female, 32.	2½ yr., renal colic.	At crossing uterine artery. Ureteral catheterization. Felt *per vaginam*.	Oval. 6 x 2.5 x 2 cm. Wt. 16.2 gms.	Extraperitoneal ureterotomy. No sutures.	Recovery.
D2 61.	Cullingworth. Tran. Lon. Path. Soc., Vol. XXXVI, 1885, p. 278.	Female, 30.	Right renal colic. Tubo-ovarian masses felt *per vaginam*.	Just above bladder in right ureter.	Not stated.	Intraperitoneal ureterotomy. Suture.	Death 80 hrs.
62.	Lane. Lancet, 1890, II, p. 967.	Female, 23.	20 yr., abdom. pain. Pyuria.	1 in. below iliac crest.	¾ in. long. Uric acid and urates.	Intraperitoneal ureterotomy. Suture.	Recovery.

	Reference.	Sex and Age.	Chief symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
63.	Roberts. Anns. of Surgery, 1895, 22, p. 363.	Female, 57.	47 yr., renal colic. Passage stones.	Level of broad ligament. Sounded from above and below.	Size of olive stone. $\frac{7}{8} \times \frac{1}{2}$ in.	Intraperitoneal ureterotomy. Suture.	Recovery.
64.	Desguin. Ann. di. la. Soc. Belg., May 1899, p. 63.	Male, 34.	29 yr., abdom. pain. Point tenderness above McBurney's point.	Level of brim of pelvis. Diagnosis bet. cal. and appendicitis not made.	Irregular. 33 x 36 mm.	Intraperitoneal ureterotomy. No sutures.	Recovery.
65.	Kelly. J. Am. M. A., May 11, 1901.	Female, 37.	8 yr., pain in right side. Nausea and fever.	3 cm. below kidney.	2 stones, each 14 mm. long.	Intraperitoneal ureterotomy. Suture.	Recovery.
66.	Sommers. Ann. of Surgery 1900. Vol. 32, p. 843.	Female, 23,	Attacks of pain in right side. Vomiting. Dysuria.	Level brim of pelvis. Radiograph. Felt *per vaginam*.	Wt. 165 mmg. Uric acid and calcium oxalate.	Intraperitoneal ureterotomy. Suture.	Recovery.
67.	Hawkes. Pres. Hos. Rep. Vol. V, 1902.	Female, 23.	2 yr., frequent micturition and hematuria.	Above level of cervix. Felt *per vaginam*.	$2\frac{1}{2}$ in long. Wt. 158 grains.	Intraperitoneal ureterotomy. Suture.	Recovery.
D3 68.	Thornton. Morris, Lancet, 99, II, p. 1652.	.....	Abdom. Neph. discovered half way down ureter.	Half way down the ureter.	Not stated.	Extraperitoneal ureterotomy combined with abdominal incision. No sutures.	Death 6th day. Pneumonia.
69.	Lloyd. Br. Med. Jour., 1896, II, p. 1206.	Female, 35.	2 yr., left lumbar pain. Hematuria.	1 inch from bladder. Nephrotomy. Sounding ureter from above.	Triangular. Size pea.	Extraperitoneal ureterotomy combined with abdominal incision. No sutures.	Recovery.
70.	Morris. Hunterian Lectures, 1898, p. 77.	Male, 32.	2 mo., pain in right loin.	At pelvic brim. Felt through abdominal wall.	Not stated.	Extraperitoneal ureterotomy combined with abdominal incision.	Recovery.
D1 71.	Emmet. Prin. and Pract. Gyn., 1884, p. 796.	Female.	Symptoms of stone in bladder.	In ureteral orifice. Felt *per vaginam*.	$\frac{17}{8} \times \frac{1}{2}$ inch. Ca. phos. and carb.	Vaginal ureterotomy. Suture.	Recovery.

	Reference.	Sex and Age.	Chief Symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
72.	Berg. Jahr. Geburt u. Gyn., 1889, p. 666.	Female.	Not stated.	In ureteral orifice. Felt *per urethram.*	Hazel nut size.	Vaginal ureterotomy. No sutures.	Recovery.
73.	Cabot. Bos. Med. and Surg. J. '90, p. 247. Am. J. Med. Sc. '92, p. 43.	Female, 39.	15 yr., L. renal colic. Tumor in L. side.	Vesical portion of ureter Felt *per vaginam.*	Elongate. Formed around two nuclei.	Vaginal ureterotomy. No sutures.	Recovery.
74.	Lowson. Br. Med. J., 1893, I, p. 11.	Female.	Pain in R. side. Tumor. Pyuria.	Just above bladder in R. ureter. Felt *per vaginam*	Long, oval.	Vaginal ureterotomy. No sutures.	Recovery.
75.	Cotterell. Br. Med. J., 1894, I, p. 1022.	Female, 44.	Symptoms of stone in bladder.	Lower end of right ureter. Felt *per urethram.*	2 stones.	Vaginal ureterotomy. No sutures.	Recovery.
76.	Doyen. Glauteney. Chir d l'uretére Paris 1895, p. 126.	Female, 21.	Symptoms of stone in bladder.	Lower end of ureter. Felt *per vaginam.*	"Chain calculi." 24 stones, 7 to 12 mm.	Vaginal ureterotomy. Sutured with silk.	Recovery.
77.	Israel. Ber. klin. Woch. 1896, p. 841.	Female, 44.	$8\frac{1}{2}$ yr., renal colic. Hematuria. Pyuria.	5 cm. above ureteral orifice.	3.5 cm. long. Size of plum pit.	Vaginal ureterotomy. Sutured with silk.	Recovery.
78.	Fenwick. Edin. Med. J., 1898, p. 28.	Female, 18.	10 yr., renal colic. Constant pain in groin.	Just above bladder. Felt *per vaginam.*	Size of nutmeg. Smooth. Wt. $\frac{1}{2}$ oz.	Vaginal ureterotomy. No sutures.	Recovery.
79.	Barling. Br. Med. J. 1898, I, p. 561.	Female, 32.	Constant abd. pain. Acute attacks nausea and vomiting.	2 in. above bladder. Felt *per vaginam.*	Not stated.	Vaginal ureterotomy. No sutures.	Recovery.
80.	Mundé. Yale Med. J., Nov. 1899.	Female, 40.	Extra ut. pregnancy. Cholecystostomy. Pyrexia. Pyuria.	Lower end of ureter. Felt *per vaginam.*	$1\frac{3}{4} \times \frac{5}{8}$ in. Grown in under surface.	Vaginal ureterotomy. No sutures.	Died.
81.	Zukerkandl. Wiener k. Woch. 1900, p. 10.	Female, 55.	18 mo., pain on urination.	In left ureteral orifice. Seen with cystoscope.	1 x 1.5 cm. Dumbbell shaped.	Vaginal ureterotomy. Fine silk sutures.	Recovery.
82.	Halsted. Jour. Am. Med. Assoc., May 11, 1901.	Female, 56.	Six attacks of left renal colic.	2 cm. from bladder. Catheterization of ureter.	1. x 0.5 x 0.4 cm. Wt. 2 grains.	Vaginal ureterotomy. No sutures.	Recovery.

	Reference.	Sex and Age.	Chief symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
83.	Israel. Loc. cit. p. 365.	Female, 64.	3 yr., pain in left side. Hematuria.	Vesical portion ureter. Felt *per vaginam.*	3 x 2.2 x .75 cm.	Vaginal ureterotomy. No sutures.	Recovery.
84.	Kelly. Jour. Am. Med. Assoc., May 11, 1901.	Female, 32.	11 yr., renal colic both sides. Pyuria.	6 cm. from vesical orifice. Wax tip catheter. Radiograph	Size of date stone. 1.8 x .8 x .8 cm. Wt. 1.25 gms.	Cœliotomy. Stone pushed down and removed by vaginal ureterotomy.	Recovery.
85.	Emmet. Loc. cit. p. 796.	Female	Symptoms of vesical calculus.	In ureteral orifice. Felt *per urethram.*	Not stated.	Cystotomy.	Recovery.
86.	Helferich. Arch. f. klin. Chir., 1894. Bd. 48, p. 875.	Male, 24.	Symptoms of vesical calculus.	In left ureteral orifice at operation.	Not stated.	Suprapubic cystotomy. 3 vesical calculi removed.	Recovery.
87.	Pitt. Morgan. Lancet, 1898, I, p. 560.	Male, 9	Symptoms of vesical calculus.	In right ureteral orifice at operation.	Pyramidal. $\frac{1}{2}$ in. long.	Suprapubic cystotomy.	Recovery.
88.	Bishop. Med. Chron. 1898, p. 429. Ed. M. J. 1899, p. 47.	Female, 35.	Many years. Left iliac pain. Oliguria.	In left ureteral orifice. Felt *per rectum.*	Hazel nut size.	Suprapubic cystotomy.	Died 3rd day.
89.	Bishop. Ed. M. J. Loc. cit.	Male, 7.	Not stated.	In right ureteral orifice. Felt *per rectum.*	Not stated.	Suprapubic cystotomy.	Recovery. Fistula.
90.	Ceci. La Reforma Med., Sept. 5, 1897.	Male.	Anuria.	Not stated.	7 cal. from L. ureter. Stone in R. ureter, found at operation.	Rectal ureterotomy.	Died 26 hrs. after operation.
91.	Fenwick. Ed. Med. J., 1898, p. 281.	Male, 18.	18 mo. Hematuria. Pro apse of ureter seen with cystoscope.	Lower end right ureter. Felt *per rectum.*	Size small peach stone. Wt 21_4 dr.	Perineal ureterotomy. No sutures.	Recovery.
92.	Godlee. Practitioner, 1887, p. 251.	Female, 30-40.	Pyuria. Hematuria.	In right ureteral orifice. Felt *per urethram.*	Oval. 1_4 in. long.	*Per urethram.* Ureter. enlarged.	Recovery.
93.	Czerny. Berl. klin. Woch. 1887, p. 777.	Female.	Vesical tenesmus and hematuria.	Lower end of ureter. Vaginal examination	Not stated.	*Per urethram.*	Recovery.

	Reference.	Sex and Age.	Chief symptoms.	Situation. How recognized.	Character of Stone.	Operation.	Result.
94.	Richmond. Trans. Med. Assoc. Missouri. 1888.	Female, 42.	Symptoms of vesical calculus.	In ureteral orifice.	Not stated.	*Per urethram.* Urethra dilated and stone dislodged with tenaculum.	Recovery.
95.	Whitehead. Br. Med. J., 1894, p. 68.	Female.	Only symptom was frequent meiturition	Lower end of ureter Comet shaped tumor palpated through vagina and abdom. walls.	11 calculi.	*Per urethram.*	Recovery.
96.	Thornton. Lancet, 1896, I, p. 92.	Female, 27.	Renal colic 7th to 17th yr. Passed calculus and was well 10 years. Colic for 10 days. Operation 6 mo. later.	Vesical portion of right ureter.	2 oval calculi.	*Per urethram.* Urethra dilated and ureteral orifice incised Intraabdominal fistula produced.	Died 13th day. Anuria. Escape of urine into abdominal cavity found *post mortem.*
97.	Hall. Personal letter. to Dr Kelly. 1897.	Female, 24.	Nephritic colic following labor. Irritable bladder with increased frequency of micturition. Hematuria.	In left ureteral orifice. Seen with Kelly cystoscope.	Not stated.	*Per urethram.* Dislodged by searcher through cystoscope.	Recovery.
98.	Freyer. Tran. Med. Soc., London, 1899, XXII, p. 102. Lancet, 1899, I, p 211.	Male, 53.	13 yr., symptoms stone in kidney. Exploratory nephrotomy. No stone found.	In right ureteral orifice. Seen with cystoscope.	Not stated.	*Per urethram.* Removed with lithotrite.	Recovery.
99.	Young. Loc. cit.	Male, 31.	Renal colic for 7 years. Retention of urine. Constant desire to urinate.	In ureteral orifice. Seen with cystoscope	3 x 5 x 7 mm. Covered with spicules.	Dislodged by ureteral catheter and Caspar's male cystoscope.	Recovery.
F 100.	Kelly. J. Am. Med. A., Mch. 3, 1900.	Female, 38.	Several attacks of renal colic.	Just above bladder. Catheterization of ureter.	Not stated.	Ureter dilated *per urethram.* Stone passed.	Recovery.
G 101.	Albarran. Ann. d. mal. d. Or. G. U., 1894. p. 193 and 845.	Male, 30.	Nephritic colic. Abscess. Sinus below. Pour. Lig.	Near pelvic brim. Probing sinus.	Not stated.	Opening of old sinus.	Recovery.

SUMMARY OF 101 OPERATIONS FOR URETERAL CALCULUS.

			Cases.	R.	D.	Mortality.
A.—*Nephrectomy.*	1.	Lumbar	3	0	3	100%
	2.	Abdominal	1	1	0	
B.—*Nephroureterectomy*			7	7	0	
C.—*Nephrotomy.*	1.	Lumbar	20	12	8	40%
	2.	Lumbar, combined with cœliotomy	2	2	0	
D.—*Ureterotomy.*	1.	Extraperitoneal	27	23	4	14.8%
	2.	Intraperitoneal	7	6	1	
	3.	Extraperitoneal, combined with cœliotomy	3	2	1	
	4.	Vaginal	13	12	1	7.7%
	5.	Vaginal, combined with cœliotomy	1	1	0	
	6.	Vesical	5	4	1	
	7.	Rectal	1	0	1	
	8.	Perineal	1	1	0	
E.—Removal of calculus *per urethram*			8	7	1	
F.—Dilatation of ureter *per urethram*			1	1	0	
G.—Removal of calculus through sinus			1	1	0	
			101	80	21	20.8

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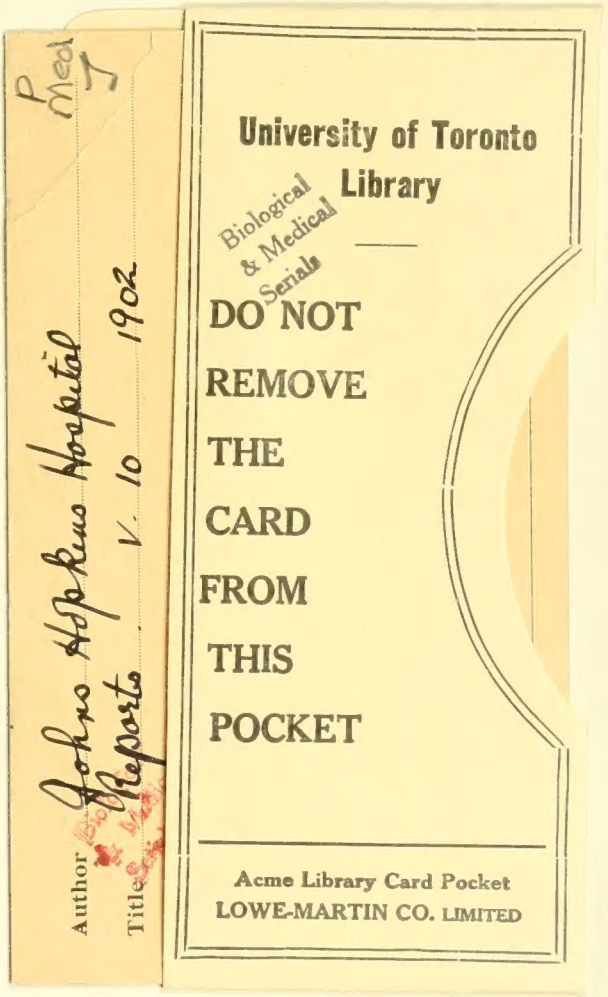
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